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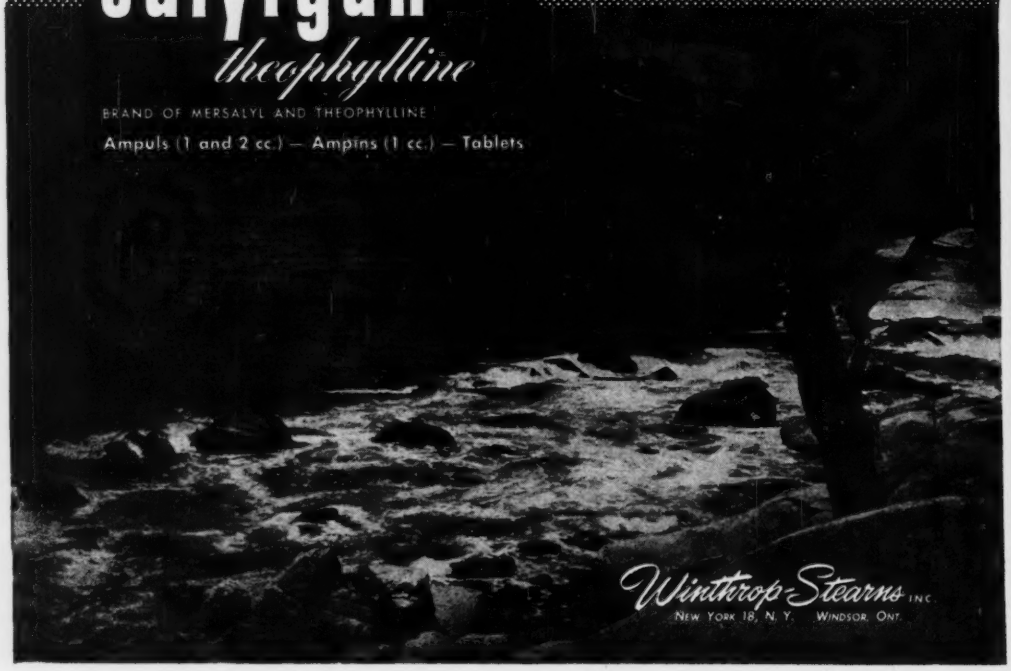

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The Effect of Vegetable Fat Ingestion on Human Serum Cholesterol Concentration

By E. A. Hildreth, M.D., S. M. Mellinkoff, M.D., G. W. Blair, M.D., and D. M. Hildreth, B.S.

In 3 healthy male physicians a reduction of dietary fat produced a significant fall in the serum cholesterol concentration. Subsequently, when a diet containing normal quantities of fat but very low in cholesterol was taken, a rise in serum cholesterol concentration occurred in all 3 subjects.

WHILE controversy has long prevailed concerning the possibility of lowering serum cholesterol by regulation of the diet,[1-3] there is now ample evidence that in most individuals the serum cholesterol concentration will fall if the intake of fat is sufficiently restricted.[3-7] Some investigators believe that the chief reason for this chemical alterations is that a low-fat diet automatically restricts the ingestion of cholesterol.[8] However, animal experiments suggest that the dietary fat level, per se, is more important than is the dietary cholesterol level in changing the serum cholesterol concentration.[9-13] Our experiments were designed to discover whether human serum cholesterol concentration can be affected by a diet low in cholesterol but of normal fat content. Since there is evidence that vegetable fats contain no cholesterol whatsoever and since sterols found in plants are not absorbed or converted into cholesterol in significant amounts by animals,[9, 10, 13] it seemed worthwhile to investigate the effect of vegetable fat on serum cholesterol concentration.

From the Department of Therapeutic Research, the Gastrointestinal Section (Kinsey-Thomas Foundation), and the Cardiovascular Section of the Robinette Foundation of the Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

This work was done while one of us (E.A.H.) was a Postdoctorate Research Fellow of the United States Public Health Service, and another (S.M.M.) was a Smith, Kline and French Fellow in Gastroenterology.

Evaluation of the effect of diet on serum cholesterol concentration requires studies over a considerable period of time. In view of the difficulties of conducting prolonged studies on patients, three of the authors served as subjects.

One of the authors (subject 2) constantly had a level of serum cholesterol which exceeded the normal. The other 2 subjects had much lower values and were always within the normal range of serum cholesterol concentration. One of the authors, a trained dietitian, designed and supervised the diets.

Therefore 3 of the authors subjected themselves to strict diets for three to eight months. Each was studied; first on his customary diet, second when both fat and cholesterol were greatly restricted, and third, when through a diet containing vegetable fats, cholesterol was restricted but fats were normal in amount. The serum cholesterol was estimated on samples taken twice weekly during these periods by a method previously described.[3] The normal range of values for this method agrees with those recently reported by Keys.[14]

The results showed that the serum cholesterol concentration was always decreased by dietary restriction of both fat and cholesterol, but that it again approached the control level when fat without cholesterol was added.

Plan of Study

The subjects kept a list of the kinds and amount of food ingested. Liquids were measured exactly in

cc., vegetables as cupsful, and more solid food as servings. At the start of the investigation, the subjects and the dietitian discussed the menus, so that the more indefinite of these measurements could be roughly standardized. Only subject 3 was placed on a weighed diet, and he only for a part of the experiment. For the experimental periods the dietitian designed the diets and supplied each person with a diet list adjusted to his taste.

The estimated composition of these diets[15, 16] is given in table 1. During the control period, 2 subjects ate what they were accustomed to have. The third (subject 2), who had a high serum cholesterol

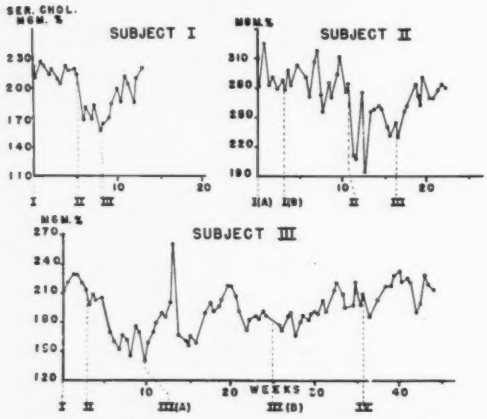

FIG. 1. Effect of diet on serum cholesterol level. *I*. Beginning of period of normal fat, normal cholesterol control diet. Subject II—I(A), 50 Gm. fat control diet; I(B), 114 Gm. fat control diet. *II*. Beginning of period of low fat, low cholesterol diet. *III*. Beginning of period of normal fat, low cholesterol diet. Subject III—III(A), normal fat, low cholesterol diet; III(B), beginning of weighed constant diet, otherwise same as III(A). *IV*. Beginning of period of second normal control diet for subject III (see text). (The roman numerals correspond to those diets so marked in table 1.)

level, had been limiting his fat intake for a year and continued so to do.

During the first test period, total fat was greatly reduced below the control level, but protein was kept unchanged, and the total calories maintained by increasing carbohydrate. The protein intake was kept as constant as possible because there are theoretic reasons for suspecting that dietary protein might also influence the serum cholesterol level.[17, 18] Had the caloric intake been altered, a confusing variable would have been present, because semi-starvation short of ketosis will lower serum cholesterol concentration.[19, 20] The body weights of these subjects were recorded daily and did not fluctuate more than 2 lbs. during the entire experiment.

RESULTS

Since each subject presented a somewhat different problem, the three sets of data will be considered separately.

Subject 1 was a white male physician, 26 years of age. There was no history of any close relative's dying or suffering from a disease attributed to atherosclerosis except in old age. Calculation showed that he selected a diet providing approximately 2500 calories and 100 Gm. of fat daily. During the 37 days on this diet (the control period) the serum cholesterol concentration averaged 217 mg. per cent (fig. 1), and fluctuated little. His diet was then changed to one containing 9 Gm. of fat daily. The serum cholesterol concentration diminished by 47 mg. per cent within five days and remained at approximately this level for 18 days, the average for this period being 170 mg. per cent. At this point 86 Gm. of vegetable fat were added to the diet while the caloric value was kept constant. The serum cholesterol concentration began to rise promptly and after 14 days approximated the original level (fig. 1). For the last 20 days of the high vegetable fat diet the control level was maintained, averaging 200 mg. per cent. However, the average value during the whole 34 days of the diet was only 192 mg. per cent, since this includes the transition figures as well as the final level attained.

Subject 2 was a white male physician, aged 30 years. Coronary artery disease and hypercholesterolemia were prevalent in his immediate family. This subject had voluntarily restricted his fat intake for the year preceding this study to the amount of 58 Gm. daily. He continued this diet for the first 20 days of this study and his serum cholesterol concentration averaged 290 mg. per cent (fig. 1), but fluctuated within a wide range. In order to test the possibility that the restricted diet taken during the year preceding the study had not lowered his cholesterol concentration, his fat intake was then raised to 114 Gm. per day. During 56 days on this diet containing a normal quantity of fat, there was no significant change in the serum cholesterol concentration, so that it is proper to condense these two periods into a single control period. In this prolonged control period

there was an average serum cholesterol level of 287 mg. per cent.

The dietary fat was then reduced to 10 Gm. per day. The serum cholesterol concentration dropped significantly, the average for this period being 241 mg. per cent, but the fluctuations in the serum cholesterol continued to be great on this low fat diet. After 37 days the diet was changed to one high in vegetable fat. This he continued for 39 days, during which 105 Gm. of vegetable fat were consumed daily. On this diet containing little cholesterol and approximately 110 Gm. of total fat this subject's serum cholesterol concentration rose to its original level.

Subject 3 (fig. 1) was a white male physician, 26 years of age, with a family history of coronary artery disease. Three members of his family, however, failed to show hypercholesterolemia when tested.

During the control period of 20 days, this subject ingested an average of 138 Gm. of fat per day (table 1) and maintained an average serum cholesterol of 221 mg. per cent (fig. 1). At the end of this period, the dietary fat was reduced to 62 Gm. for a period of 45 days. On this low fat diet the serum cholesterol level became stabilized at approximately 60 mg. per cent lower than it had been during the control diet, a highly significant difference. Finally, 70 Gm. of vegetable fat a day were added for five and one-half months. After four and one-half months on this diet, his serum cholesterol concentration did not differ significantly from the control level. While the subject was on a high vegetable fat diet the serum cholesterol rose, the average changing from 162 mg. per cent (diet II) to 206 mg. per cent (diet III).

Finding that in subject 3 the high fat, low cholesterol diet resulted in a delayed return of serum cholesterol to the control level, additional studies were made on him. First this period was continued for many months. Also, to assure ourselves that the composition of the diet was exactly known, he was placed on a constant weighed diet, eating the same foods every day. No conspicuous change in the serum cholesterol resulted, although a slow increase in serum cholesterol level is obvious in this part of the experiment (fig. 1).

Finally, to see if the control cholesterol level might have changed, a distinct possibility because of the long duration of the experiment, a final control period of 64 days was undertaken. In this the average serum cholesterol level was 213 mg. per cent.

In setting up the data for statistical analysis (table 2) there was one important consideration. Inspecting figure 1 shows that when the diet was changed the serum cholesterol level did not always respond immediately. Thus there was usually a period which in five instances lasted less than 18 days, but on one occasion continued as long as four and one-half months, until the new level was attained.

TABLE 1.—*Diet Calculations*

Subject and diet	Protein (Gm.)	Fat (Gm.)			Carbohydrate (Gm.)	Calories
		Animal	Veg.	Total		
1						
Diet I	68	60	37	97	332	2473
II	66	5	4	9	612	2793
III	65	5	90	95	356	2539
2						
Diet I (A)	62	38	20	58	265	1821
I (B)	71	100	14	114	175	2010
II	64	6	4	10	370	1826
III	66	6	105	111	240	2223
3						
Diet I	83	60	78	138	372	3062
II	84	46	16	62	529	3010
III (A & B)	84	46	92	138	369	3054
IV	80	60	80	140	370	3060

We had little interest in this transition period, and sought to compare the new level of the cholesterol concentration with the corresponding levels existing before and afterward. The decision as to when the transition period ended was usually easy. In table 2, therefore, the data have been set up in two ways. In the first method all the data obtained during each dietary period have been averaged, so that the transition period and the final level were combined, a method which has the advantage of avoiding a decision which might be regarded as arbitrary. We place more weight, however, on the statistics secured when the transition period was omitted. But indeed, except in one

instance, the changes between cholesterol levels on diets used were all significantly different by both methods. The one instance in which the difference was not significant when values of the transition period were included in the calculations was highly significant when the transition values were omitted. Therefore, we have confidence in the reality of the changes we describe.[21]

Comment

In all three cases a reduction in fat consumption was followed by a lowering of the serum cholesterol concentration. The change is very striking and statistical analysis confirms the impression that the average level on the low fat diet is significantly lower than that of the control period in all three subjects. It is worthy of note that in one subject (subject 2) a 10 Gm. fat diet lowered the serum cholesterol concentration, whereas a 58 Gm. fat diet did not. On the other hand, in subject 3, there was a significant reduction in the serum cholesterol concentration on a 62 Gm. fat diet. These findings are in agreement with our impression gained in treating a variety of patients with low fat diets, that there is considerable variation from person to person in the degree of fat restriction necessary to lower the serum cholesterol concentration. A similar impression is gained from the variable effects upon the serum cholesterol concentration in patients on the Kempner rice diet.[5]

Also, experience with patients has led us to conclude that the rate of decrease of serum cholesterol concentration is dependent on the degree to which fat ingestion is restricted. Figure 1 clearly shows that there was a slow fall of the serum cholesterol level when the diet re-

Table 2.—*Serum Cholesterol Levels under Different Diets*

Subject	Control (A)		Low Fat–Low Cholesterol Diet		Normal Fat–Low Cholesterol Diet		Control (B)		Total Control	
	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
1										
Including Transition Levels	217	7.3	170*	3.7	192*	17.5				
Omitting Transition Levels	217	7.3	170*	3.7	200*	13.4				
2										
Fat 68 Gm. Including Transition Levels	290	16.4								
Fat 114 Gm.	287	15.8	241*	25.6	270*	15.5				
Omitting Transition Levels	287	15.8	241*	25.6	278*	7.8				
3										
Including Transition Levels	221	7.6	176*	21.3	187	30.8				
Omitting Transition Levels	221	7.6	162*	9.6	206*	9.2	213	14.0	215	13.6

* The difference from the preceding mean is significant for $p = 0.05$.

striction was to only 62 Gm. per day, while there was a more rapid fall in the other subjects when their fat intakes were more severely restricted.

The marked day to day fluctuation in the serum cholesterol concentration of the hypercholesterolemic subject (subject 2) during the control period is in contrast with the relative constancy observed in the other subjects. This is consistent with the findings of Morrison and others[22] in patients with clinical evidence of coronary artery disease.

The serum cholesterol level of subject 2 did

not rise when his dietary fat was raised from 58 to 114 Gm., so evidently the 58 Gm. fat diet had not been adequate to lower his serum cholesterol value. Similarly, Turner was unable to raise serum cholesterol levels above the normal or control average by markedly increasing the fat ingestion of his patients.[23]

A diet measured by household measurements is practicable for most patients, while a weighed diet is not. Although we at first questioned the dependability of the rough measurements, it appears that this method suffices for the production of significant changes in serum cholesterol levels. As a further test of the adequacy of this method, one subject (subject 2) was placed on a weighed constant diet, giving the same fat, protein, and carbohydrate values which the rough measurements were supposed to supply. The more exact measurement was accompanied by no noteworthy change in the serum cholesterol values. This is as one might have expected from the work of O'Key and Boyden,[16, 24] who demonstrated that small day to day variations in the diet had little influence on serum cholesterol.

That the reduction in the serum cholesterol was not due to the elimination of dietary cholesterol is clear in subjects 1 and 2. Restoration of the fat in the diet without restoring the cholesterol is followed by a prompt return to the control levels. This has also been noted by Keyes in one patient.[6]

The results in subject 3 were much more gradual. When fat was restored to the diet, without cholesterol, the blood level rose significantly, finally attaining values insignificantly lower than in the control periods. Also a resumption of the control diet led to no significant change. We believe the end results secured in this subject are similar to those encountered in the other cases. Apparently in this case, as well as in subjects 1 and 2, reduction of serum cholesterol concentration on the low fat diet was not due to the elimination of exogenous cholesterol.

It seemed in these experiments that the total fat content of the diet was a more important factor in determining the serum cholesterol level than is the amount of cholesterol ingested. This hypothesis is consistent with other experiments on cholesterol metabolism. It is known that the body synthesizes cholesterol from acetate, which is made available mainly by breakdown of fat.[9, 10, 13] However, carbohydrate, and to some extent protein, can give rise to two carbon fragments which are used by the body in synthesizing cholesterol. A portion of the cholesterol so formed is excreted into the intestines.[25] Its subsequent reabsorption, together with the absorption of ingested cholesterol, appears to depend upon the simultaneous absorption of fatty acids.[12, 26] It may well be that this fatty acid–cholesterol absorption relationship, as well as cholesterol synthesized from acetate, shares in the regulation of the serum cholesterol concentration. Lowering of the fat content of the intestine may thus decrease the amount of cholesterol absorbed and also the amount of acetate available for cholesterol synthesis in the body. These may be the methods by which a low fat diet decreases the serum cholesterol concentration.

Summary

The following results were obtained in a study designed to show the effect on serum cholesterol when vegetable fat containing no cholesterol was added to a diet in which total fat had been restricted previously.

1. In three healthy male physicians a reduction in the dietary fat produced a significant fall in the serum cholesterol concentration.

2. In two of the individuals, addition of vegetable fat to the diet was associated with a rapid significant rise in the serum cholesterol, to the levels observed before fat restriction. In the third, the serum cholesterol rose much more gradually, but also attained the control values.

3. Therefore, it would seem that in these three subjects the restriction of total fat and not of cholesterol alone was probably the decisive factor in lowering the serum cholesterol concentration.

Acknowledgments

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Ventricular Fibrillation Due to Digitalis Preparations

A Review and Report of Two Cases following Intravenous Administration of Acetyl Strophanthidin

By CHARLES D. ENSELBERG, M.D., JAMES P. CROCE, JR., M.D., AND BERNARD LOWN, M.D

Contrary to expectations, there are very few substantiated clinical case reports of ventricular fibrillation attributable to digitalis preparations. Two cases, one of them fatal, are here described. The nature of ventricular fibrillation due to digitalis is different from that due to other agents. Hence it may not respond to present methods of treatment in the rare cases when opportunity for treatment exists. It is vital therefore to prevent ventricular fibrillation by the avoidance of digitalis when certain premonitory signs are present.

IT IS universally taught that the ultimate danger of digitalis poisoning is ventricular fibrillation, yet a careful search of the literature discloses very few clinical cases with electrocardiographic proof. In this communication the subject will be briefly reviewed, and 2 additional cases will be described. Both of our cases were attributable to acetyl strophanthidin, a synthetic ester of the cardiac aglycone strophanthidin.[1] This new drug acts with unusual speed after intravenous administration, producing early effects in a very few minutes and peak effects within a quarter hour; the duration of action being less than four hours.[2,3]

REVIEW OF THE LITERATURE

Since 1894 ventricular fibrillation has been known to be the cause of death in animals poisoned with digitalis.[4] This arrhythmia is reputed to be the chief cause of death in patients with digitalis poisoning.[5] Nevertheless we have been able to find only 4 cases with graphic proof reported in the literature.

Reid, in several publications,[6] described a case which occurred in a patient with auricular fibrillation who received excessive amounts of tincture of digitalis. Sudden regularization of the rhythm was shown electrocardiographically to be due to bidirectional ventricular tachycardia, which abruptly changed to ventricular fibrillation as death ensued. The fibrillatory oscillations gradually diminished in amplitude and frequency prior to final standstill. Eggleston,[7] in discussing this case, described a similar one; but the records have not been published to our knowledge.

Penati[8] reported a case in which 0.125 mg. of strophanthin was given six days after digitalis bigeminy had been noted. Several hours later the electrocardiogram showed ventricular tachycardia followed by fatal ventricular fibrillation. The delayed onset is unusual, since most strophanthin deaths occur within an hour or two after administration of the drug.[9]

Zwillinger's[10] case was one of toxicity due to digitalis and strophanthin, and exhibited paroxysms of ventricular tachycardia and fibrillation with imperceptible merging of the two arrhythmias. The fibrillatory curves display the same waxing and waning of amplitude and rate as seen in experimental animals. The paroxysms were abolished by intracardiac and intravenous injections of magnesium sulfate, but the patient died some hours later.

Tandowsky, Anderson and Vandeventer[11] have published a short strip of electrocardiogram showing small irregular ventricular fibrillatory oscillations which occurred in association with sudden death. The patient had one minute earlier received an injection of ouabain, the dose of which is not stated. The control electrocardiogram showed regular sinus rhythm with right bundle branch block and ventricular extrasystoles.

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Schwartz and Jezer[12] have described 3 patients with complete heart block and episodes of ventricular fibrillation. The latter arrhythmia could be provoked in these persons by the intravenous administration of 0.25 mg. of ouabain or 0.5 cc. Digifolin. They reproduced only one record, however, which shows very short bouts of three or four complexes resembling the first (undulatory) phase which precedes actual fibrillation of the ventricles.

Two other published cases may be considered as instances of ventricular fibrillation probably or possibly due to digitalis bodies. In one instance,[13] during routine electrocardiography the patient suddenly collapsed and died, the records showing sinus tachycardia with frequent multifocal ventricular extrasystoles succeeded by ventricular fibrillation. This patient had been taking undisclosed amounts of digitalis daily. Another case,[14] reported as an illustration of successful electric defibrillation during surgery, can be interpreted as an instance of digitalis-induced fibrillation,[15] since it followed the administration of 1.6 mg. of lanatoside C. The drug had been given because of a tachycardia occurring during induction of anesthesia.

Many instances of sudden death ascribable to digitalis preparations have been described or mentioned.[4, 16–22] The patients generally had advanced heart disease and the deaths occurred at the expected time of action of the preparations used. However, since no graphic proof is available in these cases, the implication of ventricular fibrillation in these deaths is only presumptive. It is known that patients with advanced heart disease are liable to sudden death by virtue of the disease per se.

In some reports the presumption of ventricular fibrillation is better founded because bidirectional ventricular tachycardia was demonstrated shortly before death.[23–25] This type of ventricular tachycardia is considered a forerunner of ventricular fibrillation clinically as well as experimentally.[26] Nevertheless, death may be due solely to ventricular tachycardia which may cause vascular collapse or end in standstill.[27] Indeed, the latter may be as common an event as fibrillation at the termination of ventricular tachycardia.[28]

It is interesting to note that some cases of sudden death following digitalis preparations occurred in association with profuse diuresis.[9, 20, 21, 25] Most strophanthin deaths are said to be due to overdosage or to profuse diuresis.[21] Whether the diuresis is accompanied by recirculating digitalis bodies,[29, 30] or by a possibly profound depletion of potassium which alters the response of the myocardium to digitalis,[31] it remains clear that severe diuretic action is involved in some cases of grave digitalis intoxication.

Case Reports

Case 1. A 70 year old man was admitted to New York Polyclinic Hospital in a state of advanced congestive heart failure, due to arteriosclerotic and thyrotoxic heart disease. Although he had noticed progressively increasing shortness of breath, swelling of the legs and weakness for six months, he sought no medical aid until the day of admission. Five days previously he had experienced moderately severe epigastric pain followed by vomiting.

Physical examination disclosed marked orthopnea, bulging neck veins, diffuse lung rales, moderate enlargement and tenderness of the liver, and edema of the legs. There was marked exophthalmos and a soft, diffusely enlarged thyroid gland. The heart rate was 136, the rhythm regular, and the apex beat displaced about 3 cm. to the left of the midclavicular line in the fifth intercostal space. There was a systolic blowing murmur of moderate intensity over the precordium.

Laboratory data indicated a mild anemia, moderate azotemia, normal blood sugar and chlorides, and slight proteinuria accompanied by a few red and white blood cells in the urine. Chest x-ray films showed left ventricular and generalized cardiac enlargement. The lung fields were hazy, and there was some fluid at both bases. The admission electrocardiogram (fig. 1*A*) showed auricular flutter with 2:1 A-V block, the ventricular rate being 136. Flutter waves were best seen in leads II, III and aV_F, and sharp auricular deflections were obtained in CF_2. The ventricular complexes were marked by a small Q in lead I and a QR configuration in CF_5 associated with upward bowing of the S-T segment and terminal negativity of T, indicative of recent myocardial infarction.

Within three hours of admission, despite the use of oxygen and aminophylline, the dyspnea became worse. It was clear that reduction of the ventricular rate or abolition of the flutter mechanism was vitally necessary. For this purpose acetyl strophanthidin was selected. Electrocardiograms were made just prior to administration of the drug and at short intervals thereafter. Later, when the records were

developed, it was seen that just before the injection of 1.2 mg. of acetyl strophanthidin intravenously frequent ventricular extrasystoles were present (fig. 1*B*, *C*, *D*). Two minutes after the injection, a paroxysm of ventricular tachycardia at least seven complexes long occurred, followed by extrasystoles from the same focus (fig. 1*E*). The three-minute record showed that the flutter mechanism had been replaced by a supraventricular tachycardia at a rate of 150 without A-V block (fig. 2*A*). The form of the ventricular complex was altered and there

ration, including manual pressure on the bag of the oxygen apparatus, was started at once and continued for 20 minutes. About four minutes after the collapse intracardiac needle puncture was made, but to no avail. Electrocardiograms made almost continuously showed that the fibrillation remained unchanged for about 10 minutes (fig. 2*D*). Then the rate began to slow and the amplitude of oscillations gradually diminished (fig. 2*E*). About 17 minutes after the onset of fibrillation all electrical activity ceased (fig. 2*E*).

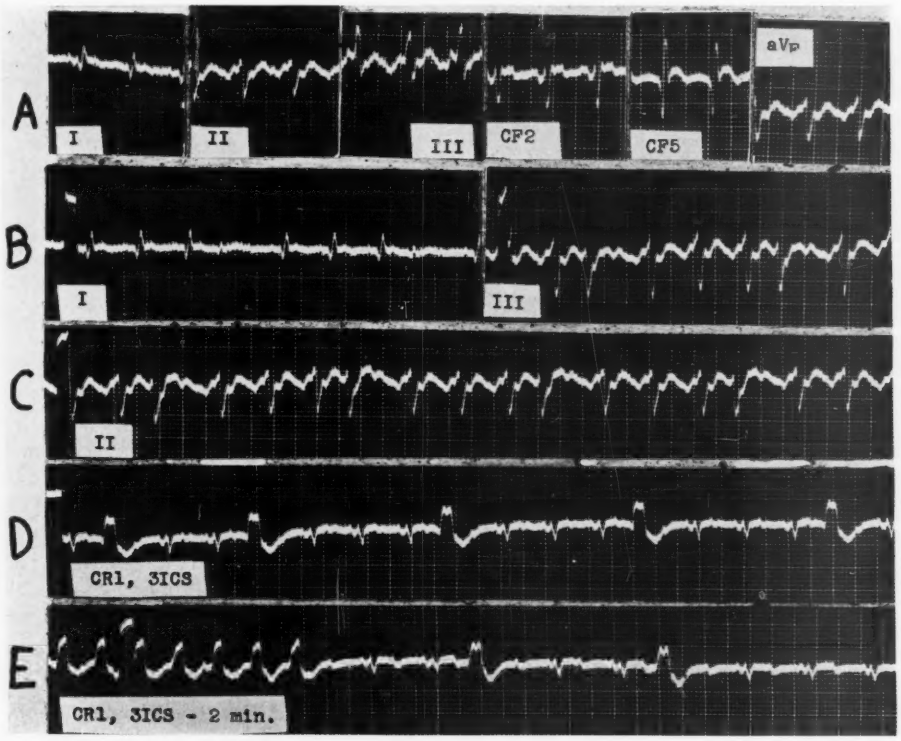

FIG. 1. Case 1. *A*, Three hours prior to acetyl strophanthidin. *B*, *C*, *D*, Just before injection of the drug. *E*. Two minutes after injection.

were occasional slightly premature (fusion) beats. Two minutes later the premature beats increased in frequency and arose from several foci (fig. 2*B*). About five and three-fourths minutes after the injection the patient suddenly cried out unintelligibly and fell back in collapse. He became strikingly pale, his eyes rolled up and he made two convulsive gasping respirations, then ceased to breathe. At this point, about six minutes after the acetyl strophanthidin, no heart sounds could be heard and the records showed a low amplitude ventricular fibrillation at a rate of about 220 (fig. 2*C*). Artificial respi-

Autopsy examination revealed chronic congestive heart failure, left ventricular hypertrophy and dilatation, and recent infarction of the left ventricle involving anterior and posterior portions of the interventricular septum. The coronary arteries were narrowed, irregular and calcified but not occluded. Microscopic examination of the thyroid showed marked hyperplasia.

Comment. In view of the history it is probable that the myocardial infarction had occurred five days before admission. It is generally felt

that there is a liability to ventricular fibrillation after myocardial infarction, particularly when ventricular extrasystoles are present,[32] or when ventricular tachycardia occurs.[33] However not all cases of ventricular fibrillation after myocardial infarction are fatal.[34, 35] Neither can it be said that all cases of sudden death in myocardial infarction complicated by ventricular tachycardia are due to fibrillation,

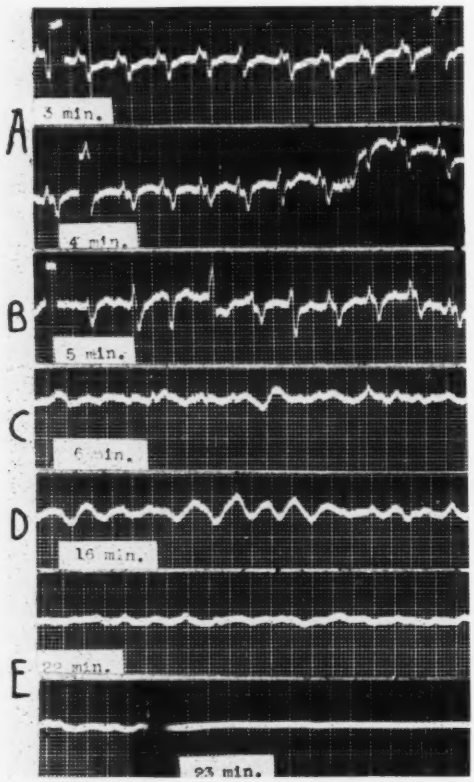

FIG. 2. Case 1. CR_I, in third intercostal space. See text.

for the tachycardia may sometimes terminate directly in standstill without going through a fibrillatory phase.[28, 36] In experimental coronary occlusion the danger of ventricular fibrillation is present in the first few minutes, and again a few days later.[37] The tissues may become prone to fibrillate under the influence of the injury potential itself, and later by virtue of the added effects of products of necrosis and sympathoadrenal discharges. The last-named could have operated in our case, since thyrotoxicosis was present.

The danger of a full dose of an intravenous digitalis preparation in recent myocardial infarction is recognized, for it may provoke ventricular fibrillation.[38] Hence small doses are advised when such preparations are used.[39] Experimental evidence indicates that the tolerance to digitalis does not change until some days after myocardial infarction, so that in three weeks ectopic rhythms are produced by about three-fourths of the dose effective in intact animals.[40] The general clinical impression is that diminished tolerance occurs earlier. In a recent case sudden death occurred one minute after 0.8 mg. of digitoxin was injected intravenously in a patient eight days after myocardial infarction.[41] In our case, the time interval was probably five days.

While it is conceivable that in our case the fatality was due only to the underlying disease, the sequence of events makes this assumption untenable. The increase in frequency of ventricular extrasystoles, the appearance of transient ventricular tachycardia, and the final development of fibrillation all occurred during the expected time of action of acetyl strophanthidin. In this case, had the character of the electrocardiogram just prior to administration of the drug been known, it might have been possible to avoid the fatality. The ventricular extrasystoles constituted a distinct contraindication to rapid digitalization.

Case 2. A 56 year old man was admitted to Montefiore Hospital because of intractable heart failure. He had suffered many attacks of angina pectoris and protracted chest pain in the preceding eight years. In the half year before admission he had increasing dyspnea and orthopnea, and generalized edema. For the past five months he was unable to take digitalis preparations because of nausea and vomiting after moderate or small doses, and mercurial diuretics had lost their effectiveness.

Physical findings on admission were striking. There was severe cyanosis, extreme distention of neck veins, profound orthopnea, a hacking cough, massive edema of the legs, some ascites, a moderately enlarged liver, and a right hydrothorax. The heart rate and rhythm were normal; the apex displaced to the anterior axillary line; and a systolic murmur of moderate intensity was heard at the apex.

Venous pressure was 200 mm. H_2O, rising to 250 mm. during pressure on the right upper abdomen. Decholin circulation time was 45 seconds, and ether time 22 seconds.

in leads I and II. QRS duration was .12 second, P-R interval 0.20 second. Precordial leads showed QS and rS deflections to the right of the transitional zone, and qr deflections in the left lateral positions.

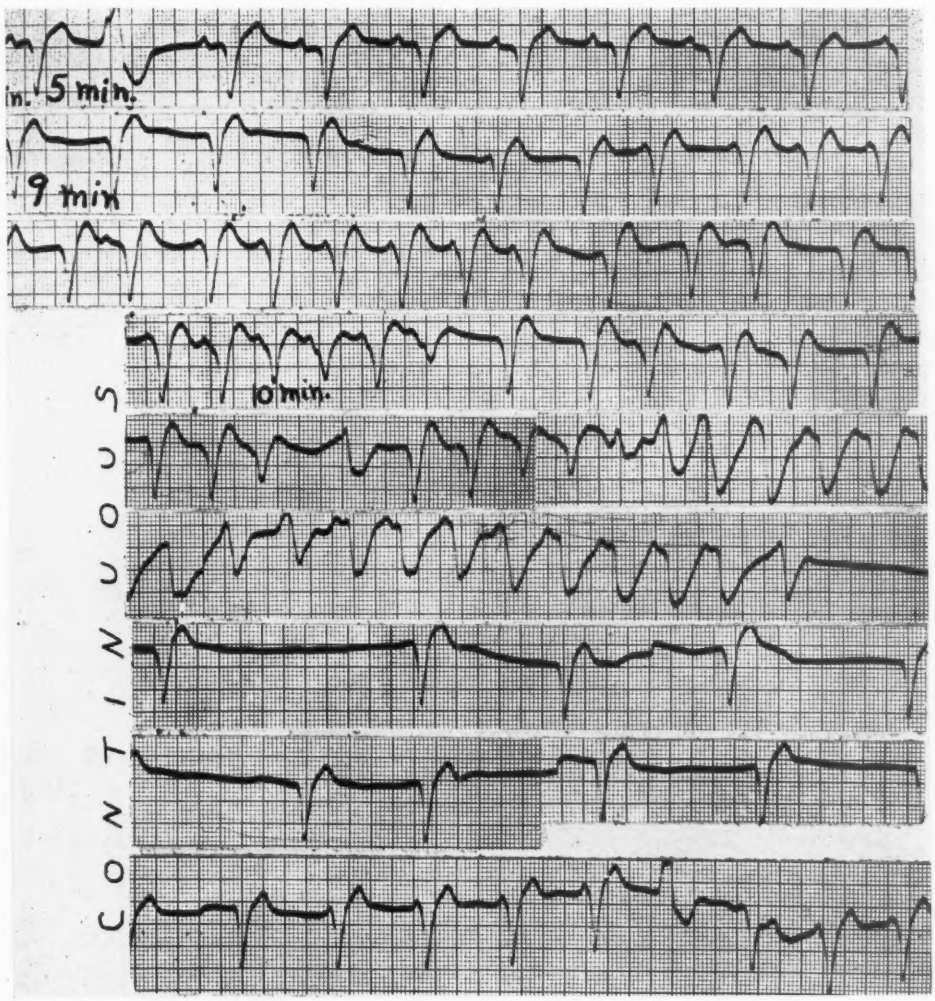

FIG. 3. Case 2. V_1 throughout. Response to 1.2 mg. acetyl strophanthidin. See text.

Laboratory examinations showed moderate proteinuria and cylindruria; slight azotemia; normal serum proteins; normal serum sodium and low chloride concentrations; serum potassium concentrations varied from 5.1 to 6.1 mEq. per liter; serum bilirubin, 1.7 mg. per 100 cc.; cephalin flocculation and alkaline phosphatase normal. The admission electrocardiogram showed low voltage of QRS groups in standard leads, with Q predominant These findings were interpreted as evidence of anterior myocardial infarction with defective intraventricular conduction.

During the first three hospital days there was slight improvement under a low sodium regime supplemented by diuretics, sedation, and almost continual oxygen inhalation. On the fourth day, 1.2 mg. of acetyl strophanthidin was given intravenously. Just before the injection, lead V_1

showed normal rhythm, a rate of 66, P-R interval 0.21 second, and QRS interval 0.14 second. The first change occurred five minutes after the drug, when a single ventricular extrasystole appeared (fig. 3, line 1). Following this the P-R intervals grew progressively shorter until they appeared to vanish (fig. 3, line 2), and later to emerge again (fig. 3, line 3). From the ninth minute on, the rhythm became irregular due to changes in both the sinus pacemaker and the lower (nodal?) center. In 10 minutes, ventricular aberration appeared and increased as the rate and irregularity increased (fig. 3, lines 4, 5). At this time the patient had severe precordial pain and a sense of great terror, wearing off as the rate suddenly slowed (fig. 3, line 7), then speeded up (fig. 3, line 9). In the next five minutes the sinus rate rose and the P waves diminished. Inspection of the 15-minute tracing shows a ventricular extrasystole after the sixth normal complex (fig. 4, line 1). This premature beat ushered in a period of prefibrillatory and fibrillatory undulations lasting 30.8 seconds (fig. 4, lines 1, 2, 3). As this period started the patient suddenly became cold, clammy and deeply cyanotic. He sank into deep

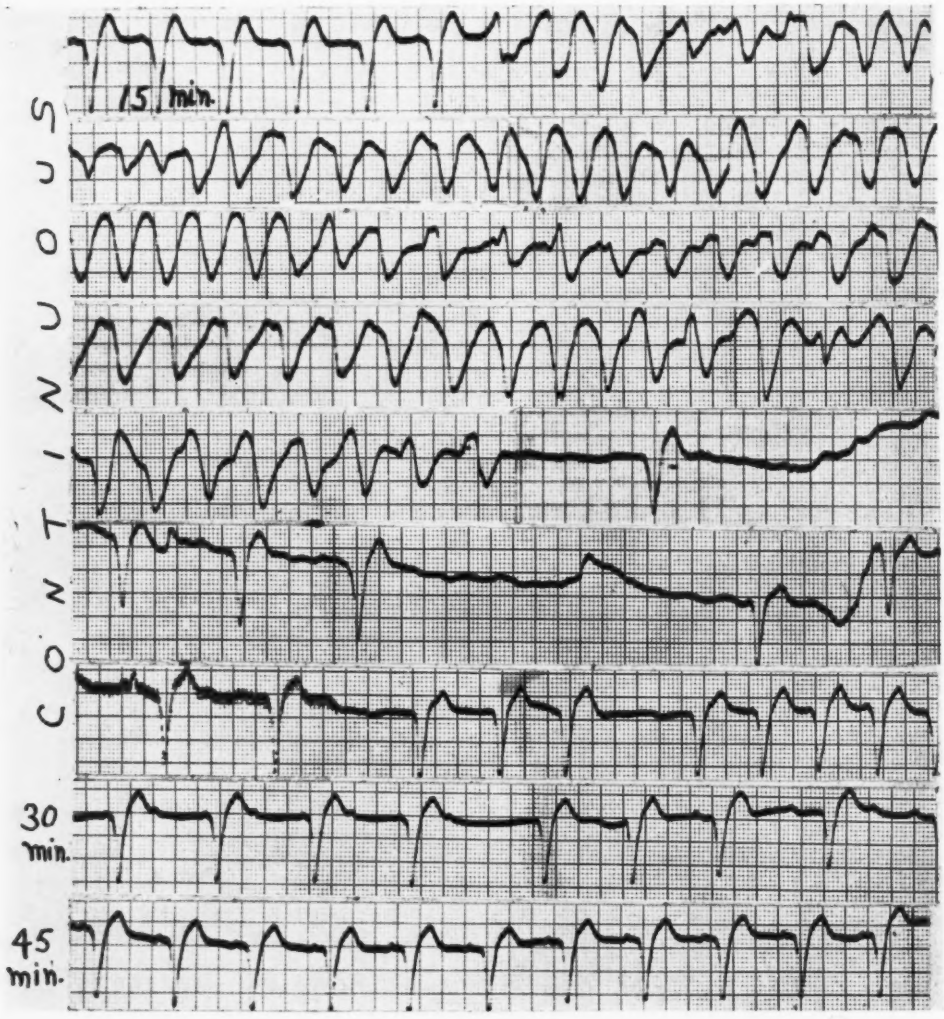

FIG. 4. Case 2. V_1 throughout. Response to 1.2 mg. acetyl strophanthidin, continued. See text.

stupor, breathing irregularly, and his heart sounds became inaudible. An oxygen mask was applied, and before other measures could be attempted coordinated heart beats returned, at first slow and irregular (fig. 4, line 5), then faster and more regular (fig. 4, line 7), the patient meanwhile rapidly recovering. For some time afterwards, there were occasional irregularities due to incomplete A-V block and sinus arrests (fig. 4, line 8). Forty-five minutes after the drug, all effects disappeared and the patient seemed no worse for the experience.

Two days later, the patient having improved further, his response to half the dose of the drug was observed. After a control observation (fig. 5, line 1), 0.6 mg. of acetyl strophanthidin was given intravenously. Again the latent period was five minutes, at which time a pair of ventricular extrasystoles appeared, followed by a nodal escape (fig. 5, line 2). Then the phenomenon formerly noted recurred; the P-R intervals seemed to diminish to the vanishing point and then reappear (fig. 5, lines 3, 4, 5, 6). Several groups of ventricular extrasystoles arose, but the disturbance did not progress to a fibrillatory state (fig. 5, lines 4, 5, 6). In 17 minutes all electrocardiographic effects disappeared. During this trial, the patient experienced only slight substernal oppression of a few minutes duration.

The patient continued to improve for a few more

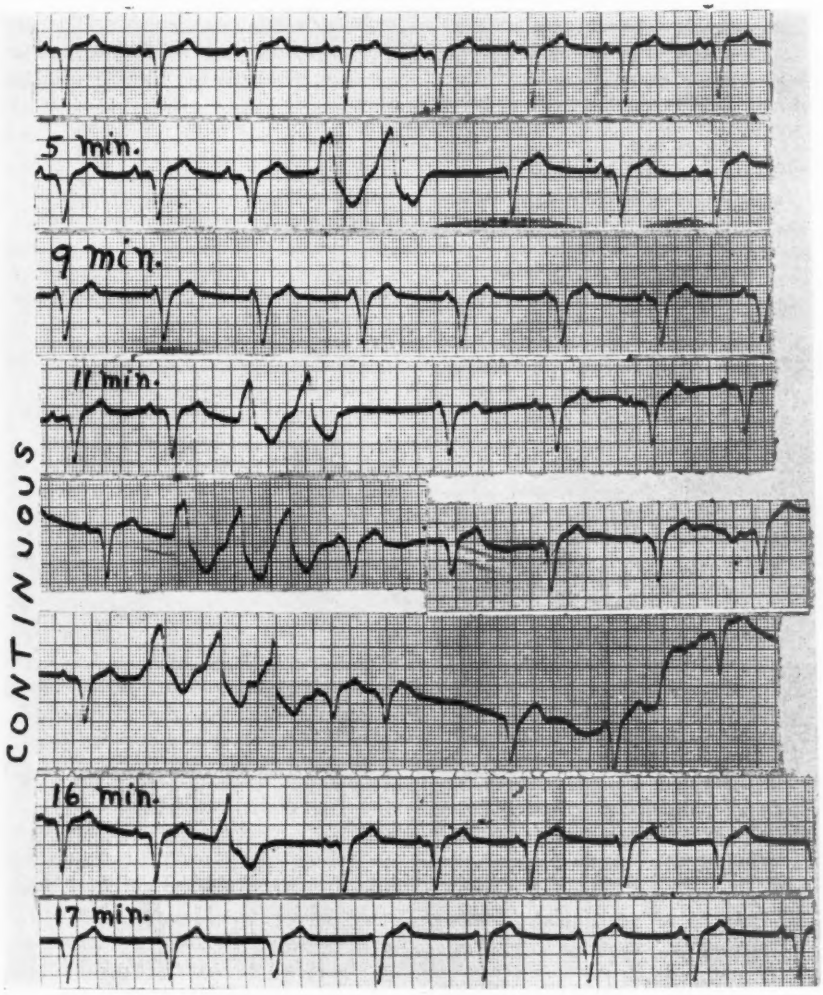

FIG. 5. Case 2. V_1 throughout. Response to 0.6 mg. acetyl strophanthidin. See text.

days. Toward the end of the second week, there was a sudden episode of intensification of cyanosis and dyspnea culminating in shock. Despite continuous oxygen therapy and plasma infusion, recovery was transient. On the fifteenth hospital day he died.

Autopsy examination revealed extreme general passive congestion and anasarca. The heart weighed 500 Gm. and was flabby and dilated. There were old and recent thrombi in the right atrium and its auricular appendage, and many infarcts of varying age in the lungs. The left ventricle was scarred by a huge area of old infarction involving both anterior and posterior walls, and there were scattered discrete scars in other parts of the left ventricle. The coronary arteries were calcified, irregular, and completely occluded in many places.

Comment. This case demonstrates the ease with which serious digitalis intoxication can occur in a patient with far advanced heart disease. It will be remembered that on many previous occasions this patient had toxic responses to oral digitalis preparations, even in reduced dosage. In animals it is known that ectopic rhythms appear after one-half to two-thirds the minimum lethal dose of digitalis, ouabain or strophanthin have been given.[42–45] In man, however, it has long been recognized that ectopic beats may occur when less than half the lethal dose has been given.[18] Cases are occasionally encountered where patients have continued or even increased their doses for long periods of time after toxic extrasystoles have appeared, yet did not succumb.

The onset of ventricular fibrillation in case 2 resembled in many respects the pattern of development of the arrhythmia in experimental animals, as discussed below. However, in addition to the ventricular ectopic activity, there was also a complex interplay between sinus and lower pacemakers. It has been noted that the development of ventricular fibrillation does not always follow the same pattern except in a general way.[46]

In the second trial, half the former dose of acetyl strophanthidin evoked a prefibrillatory state. A similar response occurred in a case reported by Robinson and Bredeck.[47] Their patient received 1 mg. of strophanthin one day after a paroxysm of ventricular fibrillation. Ten minutes later there were groups of rapid, irregular ectopic ventricular beats; two hours later, partial A-V block and frequent ventricular extrasystoles; and nine hours later, the patient died suddenly, presumably because of ventricular fibrillation.

Discussion

The Mechanism of Digitalis-Induced Ventricular Fibrillation. In cats continuously infused with digitalis the heart rate gradually slows. Before the auricular rate reaches its greatest decline, A-V dissociation appears with the ventricles beating faster than the auricles.[42] Initially the ventricular rate may be only slightly higher than the auricular.[18] This has also been noted after two-stage coronary ligation in undigitalized animals.[37] This phenomenon may explain the apparent progressive shortening of P-R intervals and disappearance of P waves in our case 2 (figs. 3, 5).

As the infusion in cats is continued after A-V dissociation has occurred, rapid and irregular beats arise from many ventricular foci. These increase in rate and aberrancy until finally fibrillation ensues.[42] At this point, the mechanical activity of the ventricles deteriorates in the fashion described so graphically by Lewis[46] and by Wiggers.[48] Cardiac dilatation accompanies the late stages.[49]

It is probable that the nature of ventricular fibrillation caused by digitalis differs from that due to other agents. The fibrillation threshold determined by electric shocks in digitalized animals is not lowered, as it is after coronary ligation.[50] Furthermore, the type of fibrillation induced in digitalized animals is different in that the oscillations are slower, more regular and more uniform. Still different is spontaneous ventricular fibrillation due to digitalis, in which various degrees of A-V block appear early, and progressive widening and deformity of ventricular complexes occurs; a pattern similar to that following toxic doses of potassium.[50] The unique nature of digitalis-induced ventricular fibrillation is also suggested by the following observations: sympatholytic agents, procaine, and quinidine protect against fibrillation provoked by electric shocks, but are ineffective in preventing ventricular fibrillation after digitalis.[51]

Despite the popular notion that ventricular

fibrillation implies heightened irritability, the disorder is most apt to occur in conditions of depression as in poisoning with digitalis, quinidine and other substances.[52] Under these conditions the heart no longer follows the "all or none law," and some parts develop local blocks which favor re-entry. The depressive action of digitalis is well known; for example, it reduces the responsiveness of the myocardium to electric stimulation.[18] This has also been demonstrated after toxic doses of strophanthin.[27] The occurrence of depressed conduction preceding ventricular fibrillation has already been mentioned. Indeed, the occurrence of A-V block emphasizes the difference between ventricular fibrillation caused by digitalis (as well as by potassium, procaine, papaverine and quinidine), and that caused by hydrocarbons and epinephrine, electric current, and coronary ligation.[53] The additive depressant effects of digitalis and quinidine may make fibrillation more likely in some cases.[54]

The Prefibrillatory State. By analogy with the development of experimental ventricular fibrillation it is possible to recognize clinically a prodromal state which could well go on to fibrillation. This was stressed by Schwensen in his report of a sudden death attributed to digitalis.[23] Just prior to death, the electrocardiogram showed bidirectional ventricular tachycardia closely resembling tracings obtained in cats under chloroform anesthesia just before the ventricles began to fibrillate.[26] Hence the tachycardia was considered to be prefibrillatory. Similarly, clinical cases have been observed which resembled digitalis toxicity in cats in the stage preceding ventricular fibrillation.[55] The usual progression of digitalis poisoning consists of the following in increasing order of severity: ventricular premature beats, coupling, polymorphism of abnormal and normal beats, salvos of premature beats, and ventricular tachycardia in paroxysms of varying length. All of these have been considered as manifestations of the prefibrillatory state.[19] As a rule these disturbances are noted only in persons with organic heart disease.[19, 56] Digitalis, even in apparently nontoxic doses, may be capable of unmasking or aggravating the prefibrillatory state in patients with advanced organic heart disease,[4, 57] as in our case 2.

In the recognition of this dangerous condition in its early stages it is important to note the association of conduction disturbances with ventricular bigeminy or multiple ectopic centers.[58, 59] Fortunately the presence of ventricular tachycardia does not always portend fibrillation, as indicated by clinical experience as well as experimental evidence.[27] It has been stated that transient ventricular fibrillation in man has never been observed without characteristic signs of a premonitory nature.[60] This statement may well be extended to apply to fibrillation due to digitalis, hence the importance of recognition of the prefibrillatory state.

Treatment. Except for the case described by Zwillinger,[10] in which intracardiac injection of magnesium sulfate abolished ventricular fibrillation, we are unaware of any successful result in a case due to digitalis. If the case of Beck, Pritchard and Feil[14] is considered as one due to digitalis (lanatoside C), then it can be said that electric defibrillation might restore a digitalis-poisoned heart.

Prevention. Since it is not feasible to treat this grave arrhythmia except by drastic methods of doubtful value (intracardiac injection of antifibrillatory drugs, surgical exposure followed by manual massage and electric defibrillation), ventricular fibrillation must be prevented at all costs. The recognition, or even suspicion, of a state of digitalis intoxication must automatically call for the immediate cessation of further digitalis therapy. If it is feared that a prefibrillatory state is present, recourse may be had to potassium[61] or procaine amide.[62] Induction of diuresis at such times should be avoided or tempered by the use of small doses of diuretic agents.

Summary and Conclusion

1. The literature on ventricular fibrillation caused by digitalis preparations was reviewed. Only 4 cases with electrocardiographic proof were found in man.

2. Two additional cases, following intravenous administration of acetyl strophanthidin, were herein reported.

3. The characteristics of digitalis-induced ventricular fibrillation were reviewed.

4. The general features of the prefibrillatory state were described. These are identical with many of the common signs of digitalis intoxication.

5. Since there is no feasible method of treatment of ventricular fibrillation due to digitalis, it must be prevented by the early recognition of the prefibrillatory state and appreciation of its ominous nature. In such cases digitalis, particularly rapidly-acting preparations, must not be used.

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The Effect of Angiocardiography on the Heart as Measured by Electrocardiographic Alterations

By Willard J. Zinn, M.D., David C. Levinson, M.D., Varner Johns, M.D., and George C. Griffith, M.D.

Six consecutive patients studied by angiocardiography or aortography ranging in age from 1½ to 68 years were checked by a direct-writer type of electrocardiograph during the procedure. The clinical entities consisted of pulmonary stenosis, coarctation of the aorta, aneurysm of the ascending aorta, ventricular septal defect (2 cases), and atrial septal defect associated with complete transposition of the great vessels. Following angiocardiography immediate T-wave depression was noted. This was followed within three minutes by the development of short bursts of ventricular tachycardia lasting up to 27 minutes after dye injection. A different and much less spectacular picture followed aortography. None of these cases showed visible distress.

THESE records are presented to bring to the attention of those doing angiocardiography the need for direct-writer continuous electrocardiographic observations during the procedure. In the field of cardiac catheterization this precaution was emphasized by Cournand, Baldwin, and Himmelstein.[1] Certainly the warnings issued in the reports of Dotter and Jackson[2] and Morgan[3] point to a need for additional precautions in performing a diagnostic procedure which has a reported mortality between 0.4 and 1 per cent! Almost half of the 26 catastrophes reported by Dotter and Jackson in their survey could easily have been sudden cardiac accidents. Biorck and co-workers[4] recently reported arrhythmias resulting from contrast media injected through an intracardiac catheter and considered their results to be due to the direct effect of the jet against the endocardium. They felt injection distal to the superior vena cava could be done without electrocardiographic control. More recently Gordon and co-workers[5] have evaluated the effect of contrast media on dogs, and in a study on the effect of angiocardiography on blood pressure by Howarth[6] brief mention was made of cardiac irregularities following injection of the dye. The incidence of such catastrophes makes it imperative to evaluate the effect of contrast media on the human myocardium.

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This work was done while one of the authors (W. J. Z.) was a National Heart Institute Trainee.

Method

Continuous tracings made with a direct-writer electrocardiograph were made during angiocardiographic and retrograde aortographic procedures. As normal leads could not be applied because of the apparatus involved in the procedures, the electrodes were so placed as to give a recognizable P, QRS, and T wave pattern. Observation was continued until a stable rhythm was reestablished or for 15 minutes after injection of the dye if no changes occurred.

Results

Six consecutive illustrative cases cited below with accompanying electrocardiograms provide ample demonstration of the effects of this procedure on the heart.

Case 1. W. B., a 7 year old Negro boy, was referred for angiocardiography with the diagnosis of a pulmonary arteriovenous fistula in the presence of associated cardiac anomalies. On Aug. 11, 1950, while under Avertin basal anesthesia, 28 cc. of 75 per cent Neo-iopax was injected into the left median basilic vein within one and one-half seconds using a 12 gage needle and a Robb-Steinberg syringe. Six films were taken at 0.7 second intervals by means of a rapid cassette changer. The angiocardiogram revealed an abnormality of the great vessels and a large atrial septal defect.

The electrocardiographic record shown in figure 1 presented immediate inversion of T waves persisting for 30 seconds. Beginning two and one-half minutes after injection premature ventricular beats appeared which soon became bigeminal. Longer and more frequent intervals of normal sinus rhythm appeared after the first 15 minutes, but basic sinus rhythm was not completely restored until 25 minutes after the injection.

The electrocardiogram (fig. 2) showed an initial bradycardia with flattening of T waves which reverted to normal within one minute. During the second minute after injection the Q-T interval was prolonged due to lengthening of the S-T segment. An apparently normal pattern was present two and one-fourth minutes after the injection, but frequent ventricular premature beats appeared within three minutes, as did a short period of sinus arrest. Bigeminal rhythm, noted three and one-fourth minutes after the injection, gave way to increasingly frequent and prolonged bursts of ventricular tachycardia arising from two alternating foci of ventricular irritability. These persisted at intervals for 16 minutes, giving way to the bigeminal rhythm 20 minutes after injection, which in turn was finally superceded by a normal sinus rhythm 27 minutes after the injection of the dye.

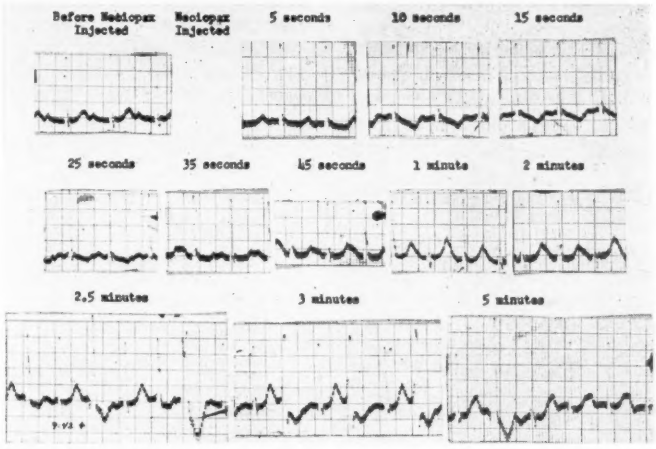

FIG. 1. Serial electrocardiographic changes during angiocardiography.

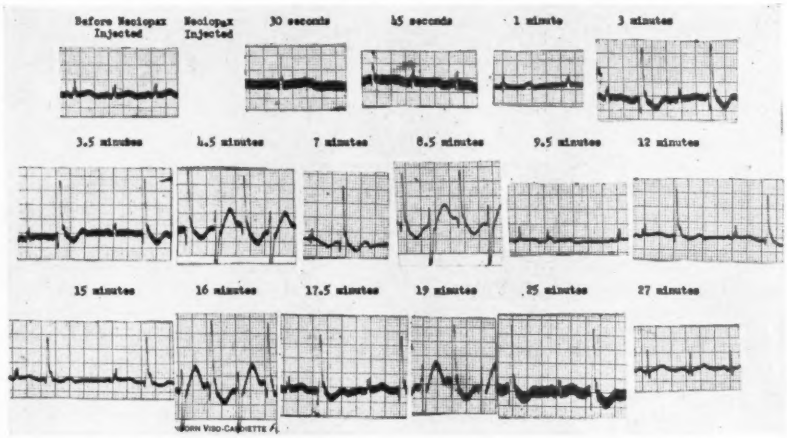

FIG. 2. Serial electrocardiographic changes during angiocardiography.

Case 2. S. D., a 1½ year old Caucasian boy, was referred for angiocardiography with the diagnosis of an interventricular septal defect. Eighteen cc. of 75 per cent Neo-iopax was injected in one second through the left basilic vein and six films were taken within four and two-tenths seconds by means of the previously described technic. No defect was demonstrated.

Case 3. A. W., a 68 year old Negro man, was referred for angiocardiography because of a mass arising beneath the right clavicle near the sternum which had been increasing in size during the past four months. The patient had an old history of inadequately treated syphilis. Although the mass resembled an aneurysm of the aorta, it could not be ascertained by either radiologic or physical examination whether this was a tumor of vascular or nonvascular origin. Two attempts were made to demonstrate the mass by angiocardiography, but on the first occasion the cassette changer became stuck and on the second study insufficient concentration of dye occurred in the left side of the circulation. On each occasion 50 cc. of 75 per cent Neo-iopax was injected within one second and six films were taken beginning five seconds after the injection at two and one-half second intervals.

The electrocardiogram taken during the first study is shown in part in the upper portion of figure 3. The lower portion shows the tracing obtained at the second examination. Prior to the second examination large doses of quinidine were administered orally at two hour intervals for a total of three doses. The first record shows the appearance of the ventricular premature beats and episodes of ventricular tachycardia as previously noted in other patients. Restoration of the sinus rhythm occurred 12 minutes after the injection of the dye. During the second study no abnormality developed during 12 minutes of continuous observation.

Case 4. B. A. S., a 2 year old Caucasian girl, was admitted for angiocardiography with the diagnosis of an interventricular septal defect. Fifteen cc. of 75 per cent Neo-iopax was injected into the left median basilic vein and six films were taken in four and two-tenths seconds. No evidence of recirculation could be demonstrated.

The electrocardiogram (fig. 4) showed immediate lowering, flattening, and inversion of T waves. A few beats showed aberrant ventricular conduction but within one minute normal rhythm was restored and the T waves were upright. The tracing was entirely normal during the next eight minutes. This patient received 10 mg. per kilogram of body weight of procaine amide orally two hours before the procedure and again just prior to the procedure.

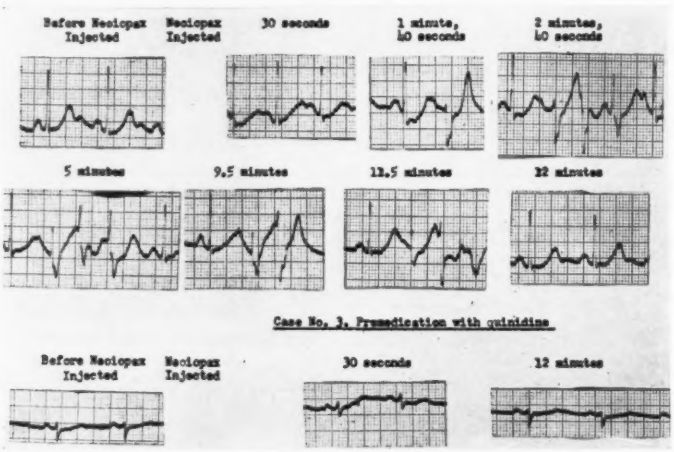

Fig. 3. Case 3. Serial electrocardiographic changes during angiocardiography. No premedication.

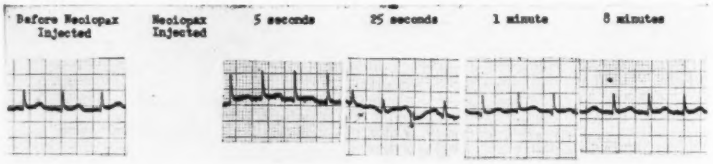

FIG. 4. Serial electrocardiographic changes during angiocardiography.

Case 5. J. A. S., a 3 year old Mexican boy (mixed strains), was referred for angiocardiography with the diagnosis of pulmonic stenosis. Prior to the procedure oral quinidine was administered in two doses two hours apart in amounts equal to 10 mg. per kilogram of body weight. Twenty cc. of 75 per cent Neo-iopax was injected in one second through the left saphenous vein. The angiocardiogram demon-

strated an interventricular septal defect with an overriding aorta.

The electrocardiogram (figure 5) showed immediate, marked depression of the S-T segment and inversion of the T wave. This returned to normal shortly, but no ventricular ectopic beats were noted although the electrocardiographic tracing was watched for 15 minutes after injection of the dye.

Case 6. D. G., an 18 year old Caucasian boy, was referred for retrograde aortography with the diagnosis of coarctation of the aorta. Forty cc. of 75 per cent Neo-iopax was injected within four seconds into the left carotid artery through a 16 gage needle. Six films were taken within four and two-tenths seconds. A hypoplastic aorta, large subclavian artery, and sharply constricted adult-type coarctation were demonstrated.

event could not readily be differentiated from cardiac or respiratory arrest since the fibrillating ventricle may be inaudible to the stethoscope and all respiratory movement may cease with the onset of syncope. Premedication with quinidine or procaine-amide appears to lessen the hazards of the procedure. It might also be expected that prompt administration of intravenous medication would terminate dangerous arrhythmias before irreversible changes had occurred.

These tracings are of particular interest in interpreting the effects of 75 per cent Neo-iopax on the human myocardium. The con

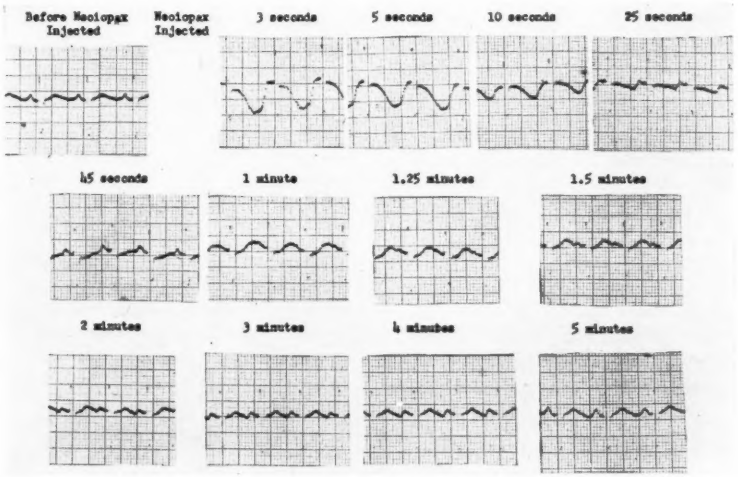

FIG. 5. Case 5. Serial electrocardiographic changes during angiocardiography. Premedication with quinidine.

No evidence of S-T segment or T-wave changes appeared on the electrocardiogram. Within forty-five seconds premature beats appeared. These were gone within one and one-half minutes and did not recur.

DISCUSSION

The illustrations amply demonstrate the need for direct electrocardiographic control during angiocardiography. The development of irritable ventricular foci could easily initiate sudden ventricular fibrillation. A second dose of dye injected into any of these irritable hearts to obtain a view in a different position, as is frequently practiced, would increase the chance of such a catastrophe. Without direct observation of the electrocardiogram such an

sistent T-wave lowering or inversion immediately following the injection suggests sudden, transient ischemia induced by the sudden increase in the load on the heart produced by literally smashing a considerable quantity of nonoxygen-bearing fluid into the heart under increased pressure within one second. Depression of the S-T segment suggesting subendodial injury was noted in case 4; in case 5 abnormality suggestive of such a change was the minor depression of J and the sagging of the S-T segment. In all instances (except when retrograde aortography was performed) the ectopic ventricular foci appeared two to three minutes after the injection. In contrast to this the retrograde injection into the aorta pro-

duced ventricular premature contractions within 30 to 45 seconds. It may be that the irritable myocardial foci develop in portions of the myocardium rendered ischemic by dye-induced spasm of smaller branches of the coronary arteries. Retrograde aortography would introduce dye more directly into the coronary ostia, but as most of the dye would pass directly down the descending aorta a far smaller amount would reach the coronary system than would be the case in angiocardiography. Angiocardiography, on the other hand, would entail a delay in reaching the coronary vessels, but the entire bolus must pass the ostia, giving a larger accumulation of dye in the smaller coronary radicles than would be the case in aortography.

An alternative explanation of the observed effects rests on the work of Broman, Forssman, and Olsson in Sweden.[7] Studying the effect of contrast media on cerebral vessels they noted a series of effects. First, increase in permeability of the vessel wall occurred. Next, local edema at the site of injury appeared. Finally they noted punctate hemorrhages in adjacent brain tissues. Of importance to the present problem they further noted that repeated nontoxic doses of dye had a summation effect, damaging the vessels by repeated subtoxic doses.

Aortography appears to affect the coronary vessels as does a single dose of dye; angiocardiography, on the other hand, in passing the whole mass of dye past the coronary ostia over a number of cardiac cycles produces the summation effect noted by Broman and his coworkers. The damage to the smaller vessels, by producing increased permeability and local edema, might produce direct myocardial irritability and thus remove the necessity of postulating vascular spasm. This explanation accounts both for the delayed onset and prolonged duration of the ectopic foci of ventricular irritability.

Conclusions

1. Immediate ischemic changes as evidenced by T-wave inversion can be induced by rapid injection of 75 per cent Neo-iopax.

2. Irritable ventricular foci are frequently produced with frequent and prolonged bursts of ventricular tachycardia. Both events are delayed in onset and may persist at least for one-half hour after the injection of 75 per cent Neo-iopax.

3. Premedication with adequate amounts of quinidine or procaine-amide may lessen the hazard of the procedure.

4. Retrograde aortography when indicated may not present as great a cardiac risk as angiocardiography, probably because far less of the contrast medium contacts the myocardium.

5. Direct-writer continuous electrocardiographic observation during angiocardiography should be maintained at all times. It must never be forgotten that the procedure is diagnostic, not therapeutic. As angiocardiography is associated with a 0.4 per cent to 1.0 per cent mortality, the procedure should be surrounded by all possible safeguards.

Acknowledgment

The active cooperation and interest in this work expressed by Dr. Ray Carter, Professor of Radiology, and by Dr. George Jacobson, Assistant Clinical Professor of Radiology, University of Southern California, School of Medicine, and by the staff of the Department of Radiology of the Los Angeles County Hospital is acknowledged.

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Studies Utilizing the Portable Electromagnetic Ballistocardiograph

I. Abnormal HIJK Patterns in Hypertensive and Coronary Artery Heart Disease

By HARRY MANDELBAUM, M.D., AND ROBERT A. MANDELBAUM, M.D.

A practical method of ballistocardiography, easily adaptable to routine office use, is described. The instrument utilized is a portable electromagnetic ballistocardiograph which records the body movements directly. One hundred normal subjects of all ages were first studied by this method. Observations upon the ballistocardiographic findings in patients with hypertensive and coronary artery heart disease are recorded; particular emphasis is placed upon a specific abnormality in the HIJK complex in the ballistocardiograms of many of these subjects.

PROGRESS in ballistocardiography is necessarily dependent upon innovations in the recording instrument. By utilizing an electromagnetic ballistocardiograph built to the electrical specifications described by Dock and Taubman[1] (fig. 1), the ballistic movements of the body can be recorded with accuracy. Our immobile examining table is covered with a portable, firm, wooden, formica-surfaced board; upon this low friction surface, the patient is placed and the ballistic pattern is recorded directly. Any nonmovable, smooth surface table that is available, however, may serve as a recording platform. This method of ballistocardiography provides an inexpensive and accurate technic adaptable to widespread clinical use.

In deciding what type of recording device to use for clinical ballistocardiography, the following considerations were weighed.[2] The original table ballistocardiographs[3] were impractical for every day clinical use because of their size and cost. The low frequency[4, 5] type of ballistocardiograph is also not suitable for routine use. Since the subjects must hold their breath during a recording, the valuable information to be gained from the respiratory variations of the ballistocardiogram is lost. Furthermore, the clinically significant L and M waves are damped out. Experimentation showed that through simple methods a high frequency ballistocardiogram could be recorded directly from a human body resting upon a hard surface. The choice then lay between a filtered photoelectric pick-up and the electromagnetic recorder. In favor of the former was its superiority in detecting the high take-off of the K wave in coarctation of the aorta; in favor of the latter was its ability to accentuate the notched J wave in myocardial and valvular disease. Against the photoelectric pick-up were the facts that bulbs and batteries must be renewed; that bulb intensity falls off gradually with age; and that adjustment is highly critical. A slight shift in the centering of the shadow on the photocell caused a large variation in the amplitude of the waves recorded. Similar shifts in centering the coil in the magnetic field resulted in less change in the amplitude of the electromagnetic tracing, and the instrument required no renewal of parts with age.

Since under the best conditions ballistocardiogram records vary with phases of digestion, with respiration, and with environmental temperature,[6] the sacrifice of convenience and day-to-day constancy of results, in order to achieve more nearly exact and linear response to body motion under ideal conditions of subject and instrument, seems unwise. From a practical as-

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pect, the electromagnetic pick-up is ideal. At a constant setting of the galvanometer, it gives standardized deflections for a given velocity of motion of the coil in relation to the magnet,

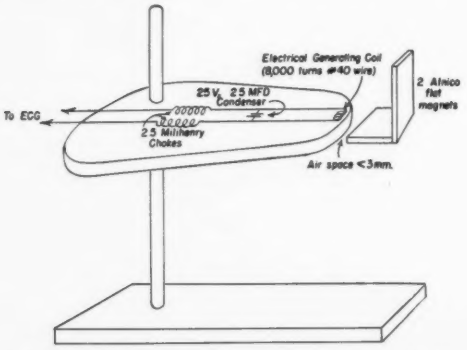

FIG. 1. The electrical format of the Dock electromagnetic ballistocardiograph.

FIG. 2. The coil of wire, which is imbedded in the most forward portion of the movable platform of the table stand, is placed in position 2 or 3 mm. away from the lowermost Alnico magnet. The light bar of wood, on which the magnets are mounted, is firmly attached by elastic bands. The patient is lying upon the formica table.

year after year. The electromagnetic type of ballistocardiograph is the most sensitive in detecting the phenomena in which we are particularly interested, in clinical ballistocardiography.

I. Instrument Standardization, Technic, and Interpretation of Records

Our instrument consists of two parts: a light bar of wood upon which a magnet is mounted, and a table stand which contains a coil of 8,000 turns of No. 40 wire connected to a resistance system, as illustrated in figure 1. The table stand, which must be of adjustable height, is constructed from a standard wooden funnel support. In our modification of the original Dock instruments,[1] the magnet bar is attached firmly across the shins by elastic bands (fig. 2). The coil of wire is placed 2 or 3 mm. away from the proximal magnet. The magnitude and the direction of the current that is induced in the coil of wire by the movement of the magnetic field is recorded by connecting the wire coil system to the lead terminals of the standard recording string electrocardiograph machine. (By mounting a horse shoe HS 2V Alnico (V) magnet upon the wooden bar, which results in a stronger magnetic field, a direct-writing instrument may serve as a recorder.) The strength of the magnetic field remains constant; the coil is always placed in the same position in respect to the magnets; and the galvanometer is always standardized so that 1 cm. equals 1 mv. The only variable is the ballistic body movement; this movement, in the horizontal plane, is reflected exactly by the magnetic bar, which is attached to the lower legs.

All resting ballistocardiograms are taken under basal conditions, which consist of 15 minutes of rest upon the table at least four hours after the last meal. The patient removes his shoes and remains lightly clothed. Hemoglobin and basal metabolism determinations are performed routinely on every subject, for marked anemia or hyperthyroidism results in an increase in amplitude in the ballistocardiogram while hypothyroidism results in a decreased amplitude. Ballistocardiograms are done on all subjects following the performance of the two step exercise test.[7, 8] The number of trips required is two-thirds of the number specified in Master's tables. A ballistocardiographic study is considered normal only if a normal pattern is found after exercise as well as at rest.

Tissue elasticity is the shaft of our ballistic pendulum. The body mass and innate tissue elasticity must play a role in determining the amplitude of the ballistic pattern obtained directly from the movement of the body on the table. Upon the configuration of the HIJK segment of the ballistic pattern, these factors have little influence, and so are of minor clinical importance. Most patients fall into the average group as concerns the body mass factors. Because we are cognizant, however, of the possible variation in amplitude, which may be produced by extremes of body mass and tissue elasticity, we have used a standardized shoulder blow produced by a weighted pendulum of specified length[1] upon our subjects during the recording. The ballistic patterns produced by these shoulder blows[9] in a footward direction are all of similar configuration but vary in amplitude from subject to subject. We have found it difficult to predict whether the movement of any subject on his viscoid subcutaneous tissue, following the shoulder blow, will be average, great or small. As a rule, obese persons have better than average "shoulder blow" ballistocardiograms, while persons beyond the seventh decade of life have a natural amplitude below the average. One would interpret a ballistocardiogram of low amplitude but normal configuration as a normal record if it is known that the shoulder blow resulted in a ballistic pattern of small amplitude. We have found it quite satisfactory in practice to substitute a sharp finger percussion of varying intensity in place of the standardized pendulum blow. These finger percussions to the shoulder in a footward direction result in deflections which, in the average subject, are more than twice the amplitude of the principal waves in the ballistocardiogram. The shoulder blow ballistic patterns provide a check upon technic. If a shoulder blow results in sharp deflections of good amplitude in association with a bizarre ballistocardiogram of low amplitude, the sharp deflections produced by percussion serve as proof that the ballistocardiogram has been accurately recorded.*

A normal ballistocardiogram (fig. 3), obtained by this direct recording of body movement, is quite similar to the normal records described by Starr.[3] In the interpretation of ballistocardiograms, we use the classification described by Brown, Hoffman, and de Lalla[10] of grade 1 to grade 4 deviations from the normal pattern. The normal ballistocardiogram can be read at a glance. A constantly recurring series of oscillations, with the HIJK complex clearly prominent and acutely defined is what we expect of a normal (fig. 3). The amplitude of the ballistic waves is measured directly from the length of the deflections as

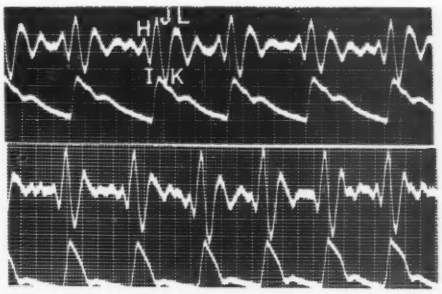

FIG. 3. J. M., male, age 32. Blood pressure 185/100. Normal ballistocardiogram, resting and after exercise. The upper record is obtained under basal conditions; the lower after the two step test. In this record, as in all others, the pulse record is made synchronously in the lower channel. The peak of the pulse wave occurs approximately at the same time as the onset of the J-K stroke. This relationship between pulse wave peak and HIJ complex is relatively constant in all ballistocardiograms.

photographed on a standard electrocardiogram film. (The string of the galvanometer is standardized in all records at 1 cm. per mv.) We have found the I–J amplitude to be approximately 10 mm. in normal subjects of all ages. The younger, athletic person tends to exceed this figure; the sedentary subject, over 50 years of age, to fall slightly below it. An I-J wave less than 6 mm. is considered abnormally low in amplitude. In a normal ballistocardiogram, the amplitude of the J-K stroke equals or is approximately 2 mm. greater than the I-J. The H-I footward deflection should be at least 4 mm. in amplitude. (These figures, of course,

* As illustrated in figures 8 and 12.

apply only to results obtained using the two Alnico flat No. 5 magnets, $\frac{7}{8} \times \frac{7}{8} \times \frac{1}{4}$ inch, to provide the magnetic field in which the above specified wire coil system moves.) Of greater importance than the actual size of the HIJK complex is the fact that it must be clearly distinguished and not equalled or overshadowed by the after waves. How little difference in amplitude exists between the inspiratory pattern as compared to the expiratory is also of definite clinical import.

II. Use on a Group of Normal Subjects

To provide a control series using this ballistocardiographic technic, records were taken on 100 consecutive subjects, in whom, by clinical examination and evaluation of history, there was no reason to suspect heart disease. Sixty-two were over 50 years of age. All blood pressure readings were in the normal range for the respective age groups. The youngest subject was 10; the oldest 75 years of age. Only 3 ballistocardiograms from the subjects under 50 years of age were considered abnormal; these 3 abnormal tracings were among the 32 records taken from presumably normal persons in the fifth decade of life. Of the 48 subjects in the sixth decade, 22 per cent had ballistocardiograms which were classified as grade 3 or 4. Another 8 per cent demonstrated grade 1 or 2 changes, particularly after exercise. Starr's[11] statistics suggest that a high proportion of these patients with abnormal ballistocardiograms will show evidence of heart disease over a 10 year period as compared with the patients with normal ballistocardiograms. Of the 14 subjects over 60, 6 had normal ballistocardiograms and 3 showed minimal abnormalities. Undoubtedly, the increased incidence of aortic rigidity, emphysema, and flabby abdominal muscular tone which accompanies aging, as well as asymptomatic myocardial changes, accounted for these abnormal ballistocardiograms in persons without evidence of heart disease.[2]

III. Ballistocardiogram in Essential Hypertension

Sixteen patients with uncomplicated essential hypertension had ballistic patterns well within the range of normal. The blood pressure range was 140/90 to 185/110 in this group of patients. The youngest was 20, the oldest 47 years of age. Urine examinations were negative, the eye ground findings were minimal, and the patients had no complaints referable to hypertension. Figure 3 is the ballistocardiogram of an asymptomatic 32 year old man, J. M. His blood pressure was 185/100. The electrocardiogram was normal. The ballistocardiogram also was within normal limits. The upper tracing was taken under basal conditions; the lower after performance of a two step exercise test.

It is our concern in young hypertensives to rule out coarctation of the aorta. The very prominent J-K stroke in this latter case was helpful in eliminating this as a cause of the hypertension. Brown and co-workers [12, 13] have shown that a short J-K stroke is characteristic of coarctation of the aorta. It should be noted that an increase in the amplitude of the J-K stroke is seen frequently in normal subjects of a tall, thin habitus[14] after having performed the two step exercise test. The I-J amplitude may remain equal to the pre-exercise I-J or increase, but not to the degree that the J-K does. An increased J-K stroke is found commonly in normal ballistocardiograms in hypertensive persons. When the J-K stroke becomes the most prominent ballistic deflection because of a proportional decrease in I-J amplitude, we have found this to be indicative of myocardial dysfunction. Dock[2] has shown that the J-K stroke may become markedly increased during the expiratory phase in ballistocardiograms taken of pregnant women. The ballistic patterns revert to normal within two weeks postpartum in these patients.

In 22 patients with hypertension, who were entirely free of complaints suggesting coronary insufficiency, but in whom there was evidence of definite vascular disease, only 2 normal ballistocardiograms were obtained. None of these patients was in heart failure. Five of these patients had electrocardiogram findings characteristic of left ventricular hypertrophy. Seven patients showed left ventricular hypertrophy and negative T waves in leads I and II, and in V_4, V_5 and V_6. Ten patients had normal electrocardiograms. The normal ballistocardiogram patterns were obtained from subjects

with normal electrocardiograms. Upon attempting to determine whether there was a specific abnormal wave pattern obtainable from patients with hypertension, we found that the ballistocardiographic abnormalities were qualitatively similar in 75 per cent of the abnormal tracings. The fact that this abnormality became more marked in the more severe hypertensive states suggests that this particular abnormality represents evidence of the effect of hypertension upon the myocardium. Actually, the abnormality in these cases depicts not the hypertensive effect upon the heart, but the heart's atypical cardiac ejection wave in response to hypertension. We apply the term "deep K stroke pattern" to describe this abnormality. Starr[3, 15] was the first to describe the deep K stroke pattern in hypertension. He called it the "late downstroke type" pattern. The ballistocardiographic findings consisted of "a shallow and indefinite I wave, followed by a slow, often fluctuating rise to J, terminated by a sharp downstroke J-K occurring late in systole and making the most prominent feature of the record."[3] Evidence was provided to show that this configuration is due to abnormal curves of blood velocity in the great vessels, the maximum expulsion velocity not being obtained until late in systole.[9] It should be noted that the diminution of amplitude of the HIJ complex is as important a factor in this abnormality as is the prominent J-K stroke. The HIJ complex is the ballistic representation of cardiac output in normal subjects. In these patients, the cardiac output does not diminish in proportion to the lessening of the HIJ wave, but merely gains its ballistic representation later in systole. Animal experiments[9] demonstrated that this type of abnormality could be produced by asphyxia. We prefer the term deep K stroke pattern rather than late downstroke pattern because of the fact that this configuration may occur as early in systole as the J-K of a normal ballistocardiogram, as indicated by the time interval between the peak of the radial pulse wave and the end of the J-K downstroke. Starr's experience suggested that this ballistic abnormality indicates serious myocardial dysfunction. This difference in amplitude between the HIJ and the J-K waves appears to be greatest in patients with long standing hypertension or those who have progressed to the malignant state, when the strain on the myocardium can be assumed to be maximum.

Figure 4 is the ballistocardiogram of A. J., a 38 year old man whose only complaint was recurrent headaches. His blood pressure was 195/110. Examination of the eye grounds showed angiospasm. The heart was of normal size on roentgen study but the configuration suggested left ventricular hypertrophy. The electrocardiogram was normal; the ballistocardiogram (fig. 4) showed normal waves under basal conditions. After performance of the two step exercise test, there was a shortening of the I-J stroke in comparison to the J-K deflection

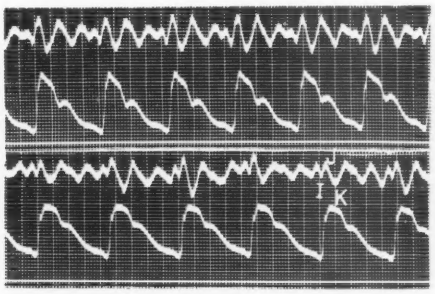

FIG. 4. A. J., male, age 38. Blood pressure 195/100. Resting ballistocardiogram normal. Two step test results in a deep K-stroke pattern and respiratory variation.

and an increased respiratory variation. This ballistocardiogram was graded 2.

The ballistocardiogram of M. G., a 40 year old woman, who had clinical evidence of malignant hypertension with no cardiac complaints, is illustrated in figure 5. An electrocardiographic study revealed left ventricular hypertrophy. The eye grounds showed hemorrhages, exudates and papilledema. The ballistocardiogram taken with basal conditions shows the prominent ballistic movement to be the downward J-K stroke. The HIJ amplitude is abnormally reduced. The principal cardiac output velocity is being generated late in systole. The precise interpretation of the large KLM complex is not certain. It may be correlated with

the auscultatory finding of a protodiastolic gallop rhythm.

Figure 6 is the ballistocardiogram of B. W., a 38 year old man, with chronic nephritis in uremia. The blood pressure was 240/140. The urea nitrogen was 130 mg. per 100 cc., and the potassium was 18.4 mg. per 100 cc. The marked difference between the amplitude of the HIJ wave and the J-K stroke is again noted. The former almost disappears in some phases. The patient was markedly anemic, and the circulation time was rapid. This probably accounts for the increased amplitude of the most prominent waves. An increased amplitude in the

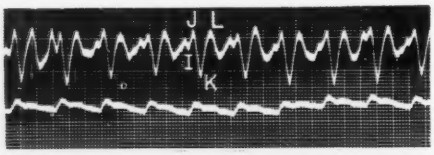

FIG. 5. M. G., female, age 40. Blood pressure 300/200. A case of malignant hypertension. Characteristic deep K-stroke pattern is seen.

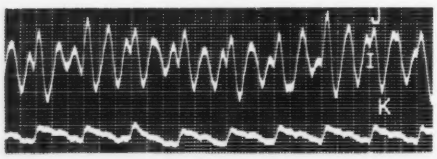

FIG. 6. B. W., male, age 38. A case of chronic nephritis in uremia. Blood pressure 240/140. Marked deep K-stroke pattern evident in basal ballistocardiogram. Extreme anemia accounts for tall complexes (characteristic of high cardiac output).

ballistocardiogram is characteristic of an abnormally high cardiac output.[9] The electrocardiogram showed minor myocardial changes.

IV. Patients with Coronary Artery Disease

The classification of Brown and associates[10] is helpful in describing the ballistocardiogram in the group of subjects with complaints of angina pectoris. Often, in this group, we have found that the only ballistic abnormality detectable is some degree of the short I-J and deep J-K stroke pattern. As is so common in coronary artery disease, this abnormality may be seen only in the expiratory phases. Furthermore, the deep K stroke pattern may be detectable only after the subject has performed a two step exercise test,[16] the increase in myocardial effort causing this pattern to appear or to become more prominent.[17] The deep K stroke ballistic abnormality is easily fitted into the gradation classification of Brown and coworkers. The abnormality in a grade 3 or a grade 4 ballistocardiogram, using this classification, is usually more bizarre than the prominent J-K stroke pattern and could suggest, in a postcoronary patient, extensive myocardial damage. (In these abnormal, bizarre patterns, the routine concomitant pulse wave record becomes of great importance in correctly identifying and interpreting the waves.) The deep K stroke pattern usually results in a grade 1 or grade 2 classification unless it is extremely accentuated. This may be the earliest ballistic abnormality in coronary insufficiency.

Of how much prognostic significance the degree of ballistic abnormality in angina pectoris is, is not absolutely certain. Many patients will have to be followed for long periods of time. Dock[2] has found that people with coronary artery disease whose ballistocardiograms are classified grade 3 or 4 according to Brown, should be given a poor prognosis on a statistical if not individual basis. While sudden death may occur in these cases, as in heart block or aortic stenosis, many may live for long periods of time. The serious significance of abnormal ballistocardiograms even in patients thought to have no heart disease is proved by Starr's statistical analysis of a 10 year follow-up.[11] He has also emphasized the good prognosis that can be attached to the finding of a normal ballistocardiogram following the healing of a myocardial infarction.[18]

The incidence of abnormal ballistocardiograms is strikingly high in our patients with symptoms suggesting coronary insufficiency. Statistically, this is the same in patients with angina who have not suffered a coronary closure as in those whose angina follows the healing of a myocardial infarction. The latter group, however, has a higher proportion of grade 3 or 4 ballistocardiograms.

In a series of 108 patients, none of whom

had suffered a coronary thrombosis, but in whom, by means of history, the diagnosis of coronary insufficiency was made, 8 normal resting ballistocardiograms were found. After performance of exercise, only one of these remained normal. These statistics are in accord with the findings of Brown and his co-workers[10] in a study of a similar group of patients. Because of the high incidence of abnormal ballistic patterns in this group of subjects, we accept the fact that an abnormal ballistocardiogram in a patient with angina pectoris is an important evidence that coronary disease is present. Thirty-nine per cent of these patients with angina pectoris had ballistocardiograms which were no worse than grade 1 resting, and 28 per cent had grade 3 or 4 resting ballistocardiograms. We cannot expect the ballistocardiogram to provide information as to which patient will develop coronary thrombosis, by the severity of the abnormality seen in the pattern. Other factors besides insufficient myocardial blood supply, such as cardiac failure, ventricular scarring, or arrhythmias may play a role in causing the abnormal pattern. Nevertheless, an abnormal ballistocardiogram is the rule rather than the exception in patients with coronary insufficiency. And as a corollary, we would be surprised to find extensive coronary artery disease in a patient, no matter what his complaints, whose electrocardiogram was normal and whose ballistocardiogram was physiologic, both at rest and after the exercise test.

The ballistocardiogram of A. S., a 55 year old obese woman, with complaints of frequent chest pain, is illustrated in figure 7. Her blood pressure was 165/100. The physical examination was noncontributory. Because of the clinical history, a diagnosis of coronary artery disease was entertained. The electrocardiogram was normal and the ballistocardiogram was physiologic. We ascribed the patient's complaints, finally, to radicular pain secondary to scoliosis of the cervical and upper thoracic spine.

In figure 8, the ballistocardiogram represented is that of a normotensive, thin 55 year old woman, R. J., with complaints of frequent substernal oppression. The electrocardiogram is normal. The resting ballistocardiogram demonstrates an expiratory diminution in the HIJ complex. After exercise, there is a diminution in amplitude and the K stroke becomes the principal deflection. The resting ballistocardiogram is classified grade 1; after exercise, it is grade 3. The shoulder percussion is recorded and shows satisfactory amplitude and configuration.

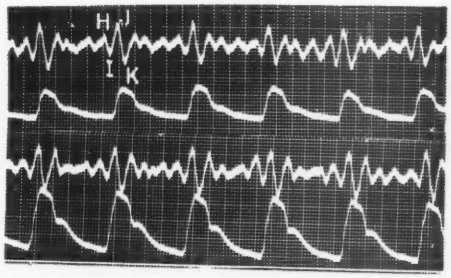

FIG. 7. A. S., female, age 55. Blood pressure 165/100. A case of chest pain due to scoliosis of the cervical and upper thoracic spine. Normal ballistocardiogram.

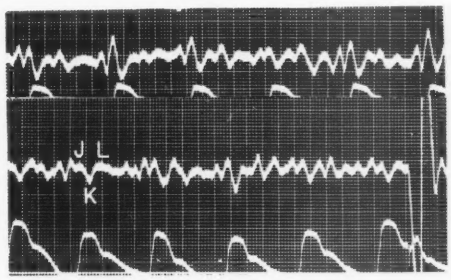

FIG. 8. R. J., female, age 55. Blood pressure 140/85. The basal ballistocardiogram shows respiratory variation. After exercise, there is a diminution in amplitude, with prominence of the K stroke. Note shoulder blow deflections.

In figure 9, we see an example of a ballistocardiogram which shows a striking deep J-K deflection pattern under basal conditions. M. S. is a 45 year old normotensive man, with left chest and shoulder pain alleviated by nitrites. The electrocardiogram shows minor myocardial changes. In this case, we find the two step exercise test resulting in a ballistic pattern which more nearly approaches normal.[17] While this improvement in pattern suggests a better prognosis, it will be necessary to follow

this group of patients, whose cardiac muscle work pattern improves with exertion, to evaluate the true significance of this finding.

In figure 10 is demonstrated an abnormal ballistocardiogram, resulting from effort. P. R. was a 44 year old normotensive white man who had been treated for peptic ulcer for many years. For the past 10 months, he had been complaining of precordial pain on effort. Repeated electrocardiograms were entirely normal. The resting ballistocardiogram is within normal limits. Exercise causes an increase in the amplitude of the inspiratory complexes, and a marked abnormality of the expiratory complexes. This marked variation of amplitude with respiration is abnormal, and is frequently seen in patients with coronary artery insufficiency and hypertensive heart disease. The physiologic causes and effects of this change in cardiac output with respiration have been investigated by Otis and his co-workers,[19] Dock[2] and Starr and Friedland.[20]

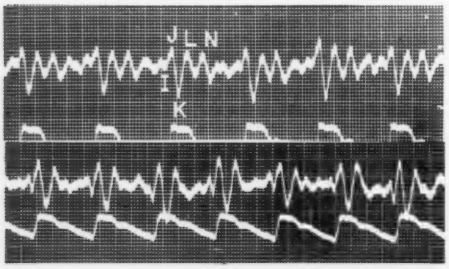

FIG. 9. M. S., male, age 45. Blood pressure 130/85. Angina of effort. The basal ballistocardiogram shows grade 1 deep K-stroke pattern. The ballistocardiogram postexercise is normal; the tall L waves give the ballistocardiogram the "late M" configuration described by Starr.[3]

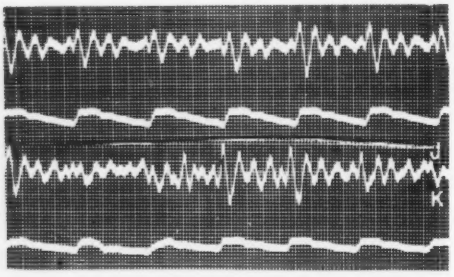

FIG. 10. P. R., male, age 44. Blood pressure 135/80. Basal ballistocardiogram normal. Effort causes bizarre waves of low amplitude in the expiratory phase, grade 2 ballistocardiogram.

The resting ballistocardiogram in figure 11 is grade 1 because of the poor amplitude in the expiratory phase. The ballistocardiogram taken immediately following the completion of a two step exercise test shows bizarre, low voltage complexes in the expiratory phase, and the deep K stroke pattern configuration in the inspiratory complexes. The latter ballistocardiogram is classified grade 3. M. B. was a patient whose complaints of angina pectoris on effort have been present for 14 months. The electrocardiogram revealed slight S-T elevation in V_1, V_2, V_3 and diphasic T waves in limb lead II, a V_R and all the V leads. In this case, the value of the exercise test in accentuating abnormalities of the ballistocardiogram is again seen. That putting the heart to work should bring out abnormal ballistic patterns in disease states, is not at all surprising. The ballistocardiograph, in a sense, records a test of heart function. Makinson,[17] in a study of the ballistocardiographic responses to exercise, found that diseased hearts usually demonstrate a combination of diminished amplitude and abnormal configuration in the ballistocardiogram, following the performance of exercise by the patient.

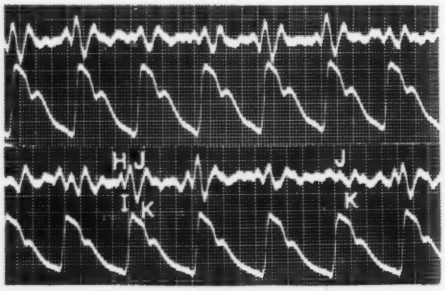

FIG. 11. M. B., male, age 56. Blood pressure 155/100. Basal ballistocardiogram grade 1. Postexercise ballistocardiogram grade 3 deep K-stroke pattern. Note bizarre expiratory complexes.

The principal wave in the resting ballistocardiogram, figure 12, is the L wave. The I-J deflection is indefinite and of poor amplitude.

The necessity for accurate identification of waves by a timing device is demonstrated clearly. After exercise, the ballistocardiogram becomes completely bizarre and unintelligible. One shoulder blow is recorded to confirm the validity of the record. The basal record is grade 3, and the exercise ballistocardiogram is grade 4. The patient, C. G., was a mild hypertensive with markedly incapacitating angina pectoris. The electrocardiogram showed minor myocardial changes and a low T_1.

F. F. is a patient with a story of weakness and angina. She had made an uneventful recovery from a myocardial infarction 18 months before this study. Repeated electrocardiograms showed findings indicative of a healed posterior wall myocardial infarction. The ballistocardiogram, figure 13, at rest, was grade 3. Exercise results in a marked deep K stroke pattern. The patient was holding her breath in expiration during this recording, which accounts for the regularity of the ballistocardiogram. It is our routine to record a section of the ballistocardiogram tracing while the patient is holding his breath in deep expiration, under basal conditions; this procedure may show an abnormality not otherwise demonstrable. On the other hand, Brown and his associates, [21] have shown that if expiratory breath holding results in a more normal ballistocardiogram in patients with angina pectoris, there is a good possibility that they will be benefited by the wearing of an abdominal binder.

M. H., age 54, is another example of a patient who had a previous myocardial infarction, and who presented himself with complaints of incapacitating angina pectoris. The blood pressure was 140/90. The erythrocyte sedimentation rate was 14 mm. in 1 hour by the Westergren method. The electrocardiogram shows evidence of a healed anterior wall myocardial infarction. The ballistocardiogram, figure 14, demonstrates maximal abnormality. It is grade 4 resting and after effort.

Extremely abnormal resting ballistocardiograms, such as figures 13 and 14, were found in 40 per cent of our 80 patients, who had survived a myocardial infarction; and an additional 20 per cent became grade 3 or 4 after performance of an exercise test. Six of these 80 patients had normal ballistocardiograms at rest. Only 3 remained normal after effort. The time interval between the coronary thrombosis and the ballistocardiographic study was greater

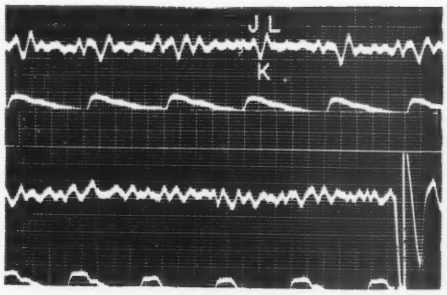

FIG. 12. C. G., female, age 53. Blood pressure 185/100. Basal ballistocardiogram grade 3. Ballistocardiogram after two step exercise is grade 4. Note shoulder blow in the latter record.

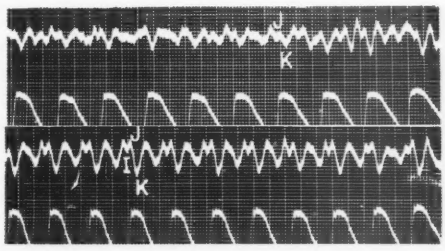

FIG. 13. F. F., female, age 53. Blood pressure 128/75. A case of healed myocardial infarction with angina pectoris. Basal ballistocardiogram grade 3. Ballistocardiogram after exercise shows a prominent deep K-stroke pattern with its associated diminution in HIJ amplitude.

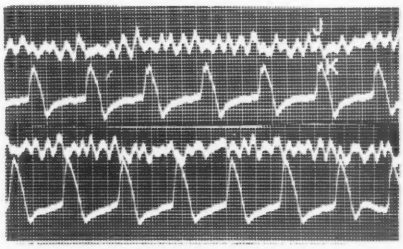

FIG. 14. M. H., male, age 54. Blood pressure 140/90. A case of healed myocardial infarction with complaints of angina pectoris. Basal and postexercise ballistocardiogram are grade 4. Without the pulse record, the prominent after waves would have been misinterpreted as IJK complexes.

than one year in 63 cases. The ballistocardiogram may prove to be a valuable prognostic guide for these patients.[22] We have noted a significant correlation between the severity of angina or incapacitation in these subjects and the degree of abnormality in the ballistocardiogram. In doing serial studies immediately after the erythrocyte sedimentation rate has returned to normal and after the electrocardiographic records show no further change, a gradual improvement in the ballistocardiographic pattern appears to parallel the patient's clinical recovery. Although some patients with persistent grade 3 or 4 abnormalities do make apparent clinical recovery, it is our impression, to date, that the postcoronary patients who develop ballistocardiograms that more nearly approach normal have the better functional recovery.

Summary

We have described our observations of ballistocardiographic patterns obtained from a large number of patients. All of the records were taken by our modification of the direct table electromagnetic ballistocardiograph of Dock. This instrument, we must stress, was designed for office and bedside use.

One hundred normal subjects were studied. Patients in variable stages of hypertension were observed. It was noted that the ballistocardiogram patterns assumed abnormalities that paralleled the severity of the hypertension and the associated changes in the electrocardiograms in the respective cases. The frequent occurrence and the significance of the deep K stroke pattern has been stressed.

The ballistocardiogram may be the only confirmatory evidence of coronary artery disease causing angina pectoris. The value of the use of the two step exercise test in ballistocardiography has been demonstrated. In our observations of patients after coronary thrombosis, we have found ballistocardiography to be helpful in evaluating the functional recovery of the myocardium.

From our experience, we feel that routine ballistocardiography is an important diagnostic and prognostic guide in the study of heart disease.

Acknowledgment

The authors wish to express their appreciation to Dr. William Dock for his invaluable assistance in all phases of this study.

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Normal Blood Pressure in the Superficial Venous System of Man at Rest in the Supine Position

By Alton Ochsner, Jr., M.D., Ralph Colp, Jr., M.D., and G. E. Burch, M.D.

The mean and range of venous pressure values in the various body surface areas is presented. Attention is directed to the variability of these values, the constantly decreasing pressure gradient towards the heart, and the essentially equal pressures in corresponding veins on opposite sides of the body. The importance of accurately identifying the vein is emphasized. The relation of venous pressure to age, sex, race and other physiologic factors is commented upon.

THIS study is concerned with measurement of the blood pressure in the superficial venous system of normal man at rest in the supine position. Physiologic variations in blood pressure in different parts of this system were recorded with the purpose of establishing values for reference.

Venous pressure was first measured in 1733, when the English clergyman Stephen Hales[13] fixed a glass tube to the left jugular vein of a thrown mare. It has been stated that Jacobson, in 1867, outlined the first series of measurements in a large number of veins,[9] but it was not until 1902 that venous pressure was first measured in man by Frey.[10] Although the contributions have been voluminous, at present there exists no comprehensive picture of the blood pressure in the superficial venous system of normal man.

Such a record is desirable in certain clinical states, such as bilateral edema and generalized venous distention, where symmetric parts cannot be compared. It is also valuable as a physiologic study in the visualization of the normal hemodynamic state, i.e., regional variations in pressure and pressure gradients in the superficial venous system. Many physicians believe that the peripheral venous pressure is uniform and still agree with Eyster and Middleton,[8] who in 1924 wrote "...we are convinced that the venous pressure in a peripheral vein in a normal subject who is at rest in bed ... rarely, if ever, rises above 11 cm. of water."

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Materials and Methods

Subjects. Subjects included 153 physicians, medical students, and ambulatory patients in the Charity Hospital of Louisiana at New Orleans. They were divided about equally between the Negro and white races and between the male and female sexes, and their ages ranged from 15 to 70 years. All subjects had normal cardiovascular and pulmonary systems, although some of the hospital patients had hernias, peptic ulcers, and small benign mammary tumors.

This investigation was carried out in the fall, winter and spring months at sea level. All studies were performed in a similar type room, in which the temperature remained about constant. With few exceptions the studies were performed in the afternoon, at least two hours after the noon day meal. All constricting clothing was removed. The patient was placed in the supine position on a hard flat examining table covered by a one-half inch pad and a one inch pillow. In general, the legs were placed together and the arms were abducted at an angle of 40 to 45 degrees but were supported on a table, and the shoulders were held in such a way that the head of the humerus was never below the suprasternal notch. The subjects were instructed to relax and breathe normally. When the pressure on the posterior surface was to be measured, the forearm was pronated, and for measurements on the anterior surface it was supinated. Slight external rotation of the arm was necessary for measurement of the pressure in the basilic vein. Measurement of the pressure in the short saphenous vein required internal rotation of the leg and slight elevation of the knee from the table. When the pressure in the jugular vein was measured,

the head was turned to the opposite side. The patient was allowed to rest for about 15 minutes while preparations were made.

Apparatus and Technic. All measurements of venous pressure were recorded with the Phlebaumanometer.*[3, 4] Its chief advantage in this study was that it permitted measurement of pressure in the small veins. The technic and use of this instrument has been described by Winsor and Burch.[3, 30] Each vein was carefully identified. The needle was always inserted in the direction of flow of the blood stream, and the adaptor was generally held so the meniscus was 2.5 cm. above the site of venipuncture. In the frontal vein of the face, however, it was necessary to have the meniscus 2.5 cm. below the horizontal level. In the jugular vein, dorsal venous arch, and marginal vein of the foot, the meniscus was about 3.5 cm. above the horizontal level.

Reference Level. The theoretic reference point is generally regarded as the right atrium, but clinically there is no constant topographic reference for this, since it varies somewhat with each individual. Although numerous levels have been proposed, the ones usually employed, for adults at least, are: (1) 10 cm. from the posterior surface of the thorax[23] and (2) the phlebostatic axis,[30] which in the supine position corresponds to the earliest proposed reference level.[28] The latter, which gives a reference point of one-half the anteroposterior diameter of the chest at the sternum, was chosen for this study. However, had the former been employed, the values would not have varied by more than 0.5 cm., since the mean thoracic diameter at the level of the sternum of all the patients studied was 21 cm. A spirit level and a ruler were employed to locate the phlebostatic level accurately.

Number of Veins and Measurements. Approximately 1400 measurements of venous pressure were recorded in 50 main channels and 60 small tributaries of the superficial venous system in 30 different locations on the surface of the body. Three to 15 determinations were made in each subject.

Results

Results of this study related to the main venous channels are summarized in figures 1 and 2 and tables 1, 2 and 3. However, certain aspects of the data deserve special attention.

Individual Values. The venous pressure varied widely over the surface of the body (figure 1, table 1). Although the pressure varied from vein to vein, the values for corresponding veins on contralateral sides of the body were essentially equal. The highest mean pressures were obtained in the frontal vein (172 mm. of water) and dorsal venous arch of the foot (188 mm. of water), the latter being higher, even in the supine position, than the mean venous pressure in the dorsal venous arch of the hand (139 mm. of water). In certain areas normal venous pressure was found to be either relatively high or low, being lower in a vein of the major venous pathway and relatively high in small tributaries of that vein.

Range of Values. Impressive was the wide variation in the values of the recorded pressures in all veins studied. Those within any one range, however, were evenly dispersed.

Pressure Gradient. A general decrease in venous pressure from the periphery towards the heart has been observed in the main venous channels of the extremities, trunk, and head and neck. However, in five areas (long saphenous vein at middle third of leg and knee, superficial epigastric vein at pubis, and cephalic vein at middle third of arm and above axilla) the mean figures in this study show a nonsignificant rise instead of a fall in venous pressure. Persistently low values were also recorded in the small veins on the anterior aspect of the wrist. Attention should be directed to the precipitous drop in venous pressure observed between the veins of the foot and the leg and between those of the hand and the forearm and the steeper gradient of pressure in the upper extremity above the wrist than in the lower extremity above the ankle (fig. 2). In the distal part of the limbs the pressure gradient of the long saphenous vein in the leg was greater than that in the veins of the forearm, whereas the pressure gradient of the long saphenous vein in the thigh was equivalent to that of the cephalic vein of the arm. Throughout the length of the upper extremity, the pressure in the basilic vein showed a sharp drop as the heart was approached.

Transient Elevation of Venous Pressure. Immediately after the small veins were punctured, a transient rise in venous pressure was noted; in all instances, however, it fell fairly precipitously rather than slowly, as had been previously observed.[30] This elevation of pressure is thought to be related to local or general contraction of the venous system.

Relation of Venous Pressure to Age, Sex and

* Phlebaumanometer, W. A. Baum Co., N. Y.

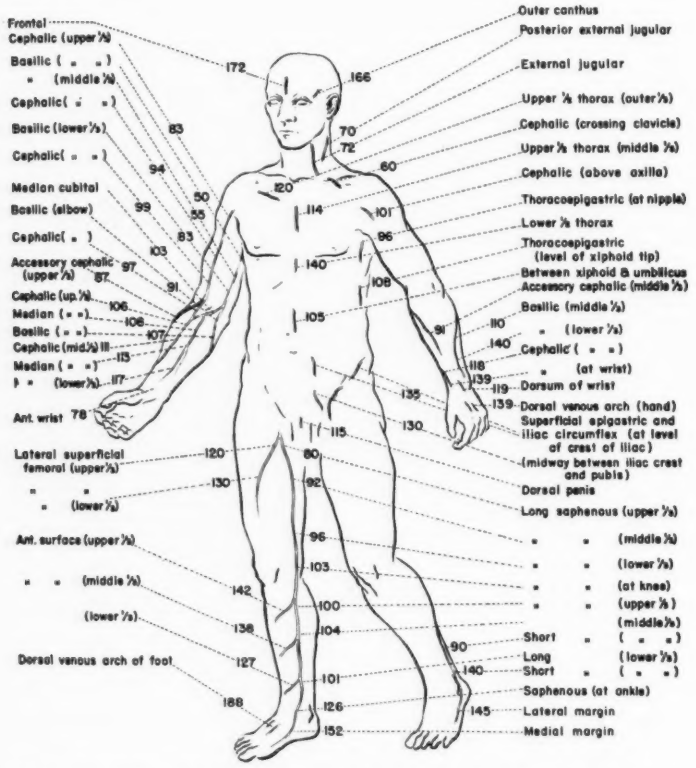

FIG. 1.—Mean normal blood pressure (mm. of water) in the superficial veins of man at rest in the supine position.

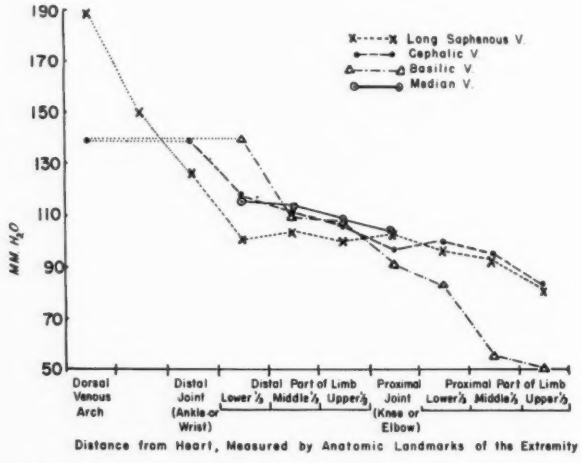

FIG. 2.—Comparison of the blood pressure gradient in the large superficial veins of the upper and lower extremities of normal man at rest in the supine position.

TABLE 1.—*Venous Pressure in Main Venous Channels of Normal Man*

Site of Venipuncture	Venous Pressure			Site of Venipuncture	Venous Pressure		
	Number of Subjects	Range mm. H_2O	Mean mm. H_2O		Number of Subjects	Range mm. H_2O	Mean mm. H_2O
Head and Neck				Lower half of thorax			
Vein at outer canthus of eye	6	125–190	166	Middle third	3	135–145	140
Frontal	25	135–230	172	Thoraco-epigastric			
External jugular	33	40–150	72	Level of nipple	9	55–135	96
Posterior external jugular	6	35–115	70	Level of xiphoid tip	10	65–150	108
Shoulder				Veins between xiphoid and umbilicus	1	105	
Cephalic vein crossing clavicle	2	60		Superficial iliac circumflex and superficial epigastric			
Cephalic vein above axilla	3	90–115	101	At the level of the iliac crest	22	85–180	135
Upper Extremity				Half way between iliac crest and pubis	10	95–180	130
(A) *Arm*				Level of pubis	3	145–170	156
Upper third				*Penis*			
Cephalic vein	11	55–140	83	Dorsal vein at base of penis	19	75–150	115
Basilic vein	6	45– 55	50	*Lower Extremity*			
Middle third				(A) *Thigh*			
Cephalic vein	25	55–140	94	Upper third			
Basilic vein	5	45– 65	55	Lateral superficial femoral	9	85–145	120
Lower third				Long saphenous	3	75–85	80
Cephalic vein	13	50–145	99	Middle third			
Basilic vein	14	50–110	83	Lateral superficial femoral	3	115–145	130
(B) *Elbow*				Long saphenous	10	50–150	92
Cephalic vein	17	65–155	97	Lower third			
Basilic vein	9	70–135	91	Long saphenous	10	50–150	96
Median cubital vein	30	60–160	103	(B) *Knee*			
(C) *Forearm*				Long saphenous	4	90–125	103
Upper third				(C) *Leg*			
Cephalic vein	12	65–150	106	Upper third			
Accessory cephalic vein	2	60–115	87	Anterior surface veins	10	75–180	142
Median antibrachial vein	10	70–135	108	Long saphenous	25	60–130	100
Basilic vein	11	70–155	107	Middle third			
Middle third				Anterior surface veins	12	100–190	138
Cephalic vein	10	70–155	111	Long saphenous	13	70–135	104
Accessory cephalic vein	3	60–130	91	Short saphenous	2	80–95	
Median vein	10	75–165	113	Lower third			
Basilic vein	11	75–150	110	Anterior surface veins	7	105–160	127
Lower third				Long saphenous vein	9	75–135	101
Cephalic vein	13	90–190	118	Short saphenous	2	110–180	
Median vein	8	65–170	117	(D) *Ankle*			
Basilic vein	1	140		Long saphenous	11	75–195	126
(D) *Wrist*				Short saphenous	0		
Cephalic vein	7	90–185	139	(E) *Foot*			
Vein on anterior aspect	8	60–100	78	Medial marginal vein	9	110–180	152
Vein on dorsum	15	80–165	119	Lateral marginal vein	7	60–230	145
(E) *Hand*				Dorsal venous arch	26	135–260	188
Dorsal venous arch	41	75–190	139				
Trunk							
Upper half of thorax							
Outer third	8	75–145	120				
Middle third	7	90–140	114				

Race. These data, summarized in tables 2 and 3, suggest that venous pressure does not vary with age except after the fifth decade, when it tends to decline. Most observers have found no change in venous pressure with age in recumbent adults.[1, 8, 11, 17, 19, 21] Hooker,[16] on the other hand, observed a progressive increase with age. Holbrook[14] noted the venous pressure to be lower after the age of 30 years, and Criep[5] found an increase in venous pressure up to 35 years, followed by a decrease to the fiftieth year. Decrease in venous pressure in the aged may possibly be related to a decline in tissue turgor.

These observations also suggest that venous pressure may be higher in women, although the number of observations is not sufficient to justify a definite conclusion. Investigators are not in general agreement about the relation of venous pressure to sex. Allen and Hochrein[1] and Jacques[18] found no relation to sex, although most authors[2, 11, 15, 22, 23, 27, 30] report slightly lower values for women. No relation to race has been observed.[30]

Relation to Miscellaneous Physiologic Factors. These observations agree with others that there is no consistent relationship between venous and arterial blood pressures[1, 6, 7, 12, 14, 18, 21, 24, 25, 29] or heart rate.[5, 15, 17] However, individuals with relatively low systolic and/or diastolic pressures tended, as a group, to have venous pressures slightly higher than the mean. In agreement with previous reports, no constant relationship was found between venous pressure and height and weight[19] or body surface area.[5] Subjects in the low weight group (below 105 pounds) tended to have low venous pressures and those in the high weight group (greater than 200 pounds) had venous pressures exceeding the mean. Higher levels have been noted in obese individuals.[5, 7, 20, 26] In a chest with a large anteroposterior diameter (greater than 25 cm.) the mean venous pressure was slightly lower than the over-all mean,

TABLE 2.—*Variations of Venous Pressure in Relation to Age*

Site of Venipuncture	Age in Years							
	15–30		31–40		41–50		51–70	
	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O
Frontal	4	195	3	193	8	162	10	179
Jugular	11	81	8	73	8	71	6	68
Antecubital area	23	104	7	87	15	102	11	101
Dorsal venous arch (hand)	18	143	7	144	11	142	5	130
Long saphenous (upper third of leg)	4	93	6	108	6	103	9	94
Dorsal venous arch (foot)	9	182	7	186	8	198	2	145

TABLE 3.—*Variations in Venous Pressure in Relation to Sex and Color*

Site of Venipuncture	Sex				Color			
	Male		Female		Negro		White	
	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O	No. of Subjects	V.P. mm. H_2O
Jugular vein	17	71	16	81	23	72	10	83
Antecutibal area	36	99	20	105				
Median cubital vein	20	99	10	106	18	103	12	103
Dorsal venous arch (hand)	27	138	14	139	22	141	19	137
Long saphenous (upper third of leg)	23	99	2	105	11	105	14	96
Dorsal venous arch (foot)	12	182	14	195	14	189	12	185

within a large chest with a small anteroposterior diameter (less than 25 cm.) the mean venous pressure was slightly higher than the over-all mean, but these differences are not significant.

and in chests of small diameter (less than 18 cm.) the mean was slightly higher than the over-all mean. As previously reported,[19] no seasonal relationship of the venous pressure was detected.

Discussion

Because of the wide range in venous pressure in various veins of the body, it would be desirable to obtain more measurements in certain areas. These wide variations in pressure must be fully appreciated when single values are applied to physiologic or clinical problems. They indicate the need for comparing values recorded at frequent intervals throughout illness and during convalescence and for comparing measurements on opposite sides. In this connection it is well to remember that the pressure in corresponding veins on opposite sides is normally essentially equal.

Extreme variations in mean venous pressures have been noted by others. Because of differences in method and reference levels, it is difficult to compare these values or to add them to the present study. In general, the values obtained in this study agree with those already reported in the literature. Previous observers, however, have neglected to study many of the veins on the surface of the body, which limits the number of veins that can be compared.

The importance of identifying the vein in interpretation of venous pressure should be emphasized. These studies show that the pressure in the small tributaries of the large collecting veins or main venous channels is definitely higher than that in the larger veins in the same area. Failure to identify the veins accurately in a given area may, therefore, lead to erroneous interpretations of data. It is well to remember that the level of the venous pressure tends to correlate with the "vascular" distance (in a physiologic sense) more than with the linear distance from the heart.

Determinations of venous pressure in the many superficial veins of normal man may be of assistance in management of clinical problems involving edematous states and diseases of the vascular system. These data are especially valuable in understanding physiologic problems related to the venous system. It is, however, only with greater interest in the venous system, hemodynamic phenomena and, more especially, in venous pressure that the many remaining gaps in knowledge concerning the venous system in normal and abnormal states will be filled. Because of the wide variations in venous pressure it is necessary to apply the values recorded in table 1 and figure 1 with caution and adequate deliberation.

Finally, it should be mentioned that measurement of venous pressure by a direct method such as this is almost devoid of complications. Occasionally a minute vein was lacerated with formation of a small hematoma, but no complicating phlebitis or thrombosis occurred.

Summary

A somewhat comprehensive picture of the blood pressure in the superficial venous system of man at rest in the supine position is presented. The study has indicated the extreme variability of venous pressure over the body surface, the wide range of venous pressure in any one area (about 100 mm. of water), the constantly decreasing pressure gradient from the periphery to the heart, the essentially equal pressures in corresponding veins on opposite sides of the body, and the importance of identifying the vein accurately during interpretations of venous pressure values. No correlation of venous pressure with age or race was found, but it seemed to be slightly higher in women.

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The Effect of Local Application of Glyceryl Trinitrate (Nitroglycerine) on Raynaud's Disease and Raynaud's Phenomenon

Studies on Blood Flow and Clinical Manifestations

By MARTIN S. KLECKNER, JR., M.D., EDGAR V. ALLEN, M.D., AND KHALIL G. WAKIM, M.D.

The authors investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud's disease and in 8 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis (3 cases), chronic occlusive disease of the arteries (3 cases), occupational disease of the arteries (1 case) and livedo reticularis (1 case). The inunction almost invariably caused an increase in the blood flow and in the skin temperature of the digits in the 14 cases of Raynaud's disease.

EPISODES of various combinations of pallor, cyanosis and rubor of the skin of the extremities resulting chiefly from exposure to cold constitute the syndrome recognized as Raynaud's phenomenon and Raynaud's disease. When these episodes of discoloration are secondary to organic disease, the correct designation is "Raynaud's phenomenon"; in the absence of an organic disease to which such episodes are secondary, the designation should be "Raynaud's disease."[1, 2] The disease most commonly associated with Raynaud's phenomenon, in our experience, has been acrosclerosis (scleroderma of the acral parts). However, this phenomenon may be associated with occlusive arterial disease, with cervical rib, with organic neurologic diseases and, infrequently, with a number of other pathologic conditions. Clinical investigators differ on the explanation of Raynaud's disease. Some believe that it is the result of an abnormality of sympathetic innervation, while others believe that it is due to a fault in the digital arteries.[3-6] Medical management has included residence in a warm environment, the use of a variety of drugs to relieve arteriolar spasm, abstinence from smoking, and treating associated conditions such as the menopause, anemia and anxiety neurosis.[7] Our experience in the treatment of Raynaud's disease with a variety of drugs has been unsatisfactory. Even residence in a warm climate may be ineffective because color changes may occur when the environmental temperature is relatively high. Some of the newer adrenolytic and ganglion-blocking drugs have been reported to be useful in the treatment of Raynaud's disease and Raynaud's phenomenon, but the action of these drugs is uncertain and, in our experience, they are of little or no practical value.

So far, sympathectomy is the most satisfactory method of treatment of Raynaud's disease.[8, 9] This operation cures Raynaud's disease of the lower extremities, but interruption of the sympathetic nerve supply of the upper extremities produces results which range from good to unsatisfactory.

In general, what we have written about the treatment of Raynaud's disease is applicable to Raynaud's phenomenon except that the results of treatment, particularly when this phenomenon is associated with acrosclerosis, are even less satisfactory.

Recently, Lund[10] has reported 30 cases of arteriosclerosis obliterans in which improvement occurred after about 0.5 to 1 Gm. of 1

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per cent glyceryl trinitrate ointment had been rubbed repeatedly on the affected parts. Increased warmth, diminution of pain, improvement in consistency of the tissues, shedding of gangrenous tissue and improvement of ulcers of the affected extremity were noted. In addition, this treatment produced varying signs of improvement in 13 cases of intermittent claudication, in 3 cases of chilblains and in 17 cases of Raynaud's disease. Lund said that this treatment deserves further consideration since sympathectomy fails to cure Raynaud's disease of the fingers in a high percentage of cases. Fox and Leslie[11] recently reported a case of Raynaud's disease and a case of acrosclerosis in which the patients were successfully treated with topical application of 2 per cent glyceryl trinitrate in lanolin 3 times a day for long periods. There was not only persistent improvement in the subjective symptoms, but studies of the temperature of the skin and oscillometry demonstrated increased blood flow to the treated digits.

Our interest in the topical application of glyceryl trinitrate was stimulated by Dr. A. W. Adson, who suggested this treatment to Fox. We investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud's disease and in 8 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis (3 cases), occlusive disease of the arteries (3 cases), occupational disease of the arteries (1 case), and livedo reticularis (1 case).

Since glyceryl trinitrate ointment is expensive and cannot be prepared by most druggists and chemists, we also studied in a limited manner the effects of inunction with ointments prepared with Priscoline (2-benzylimidazoline hydrochloride), Etamon chloride (tetraethylammonium chloride), Mecholyl chloride, histamine diphosphate, and nicotinic acid. These drugs are known or presumed to improve the blood flow in peripheral vessels. Priscoline is an adrenolytic drug. When it is administered in sufficient doses, it blocks the sympathetic vasoconstrictor motor pathways, possibly at their termination in smooth muscle. It has been reported that the oral or parenteral administration of this drug improves the blood flow in the peripheral vessels. The results which other authors[12, 13] have obtained with this drug in cases of Raynaud's disease, chronic occlusive disease of the arteries and causalgia have been encouraging.

Etamon chloride acts on the ganglions of the autonomic nervous system.[14, 15] When it is administered intravenously or intramuscularly, it causes an increase in the blood flow in the peripheral vessels. Mecholyl chloride causes dilatation of the peripheral arterioles when it is administered subcutaneously, intramuscularly, or by iontophoresis. It has been only partially effective in the treatment of Raynaud's disease, chronic occlusive disease of the arteries, and varicose ulcers. Histamine diphosphate dilates the capillaries, apparently independently of capillary innervation, and improves the blood flow. The administration of therapeutic doses of nicotinic acid to human beings causes general transient vasodilatation, probably by direct action on the blood vessels. It also causes a substantial increase in the skin temperature and in the blood flow in the peripheral vessels. The most prominent effect of the nitrites is antispasmodic. This effect results in dilatation of the small blood vessels, particularly the capillaries and venules.[16] When glyceryl trinitrate is administered sublingually in the form of tablets, it causes vasodilatation which lasts for about 30 minutes.

After we had completed the pharmacologic phase of our study, we decided to investigate the therapeutic effect of repeated inunction with the glyceryl trinitrate ointment on the episodes of discoloration of the skin which are characteristic of Raynaud's disease and Raynaud's phenomenon. Accordingly the drug was administered in this manner in 15 cases of Raynaud's disease and in 10 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis (7 cases), occupational occlusive disease of the arteries (2 cases), and thromboangiitis obliterans (1 case).

Method of Study

In order to determine the effects of glyceryl trinitrate ointment on blood flow in the extremities, a plethysmograph with a compensating spirometer recorder was employed.[17] The temperature of the fingers and toes was recorded galvanometrically.[18] The patients omitted the meal prior to coming to the laboratory, where they lay quietly on a bed in a constant temperature room for at least half an hour after the plethysmographs were applied. For the determination of blood flow to the extremities, plethysmographs were applied to the legs and to the forearms. In selected cases in which it was desirable to determine blood flow in the hands only, special hand plethysmographs were used. After the period of adaptation to the environment, the control values for the blood flow and skin temperature were established. The plethysmographs were then opened and the thermocouples were removed. The fingers and toes of one side were rubbed with the glyceryl trinitrate ointment for about three minutes and the corresponding parts of the opposite extremities were rubbed simultaneously with the lanolin base only, for the same period. The ointment remained on the toes and fingers for 20 minutes, and it was then removed. Determinations of the blood flow were again made, 30, 45 and 60 minutes after the ointment was applied.

Results of Study of Blood Flow and Skin Temperature

Table 1 shows the effect of inunction of the fingers and toes with 2 per cent glyceryl trinitrate in lanolin on the blood flow in the forearm and leg in 3 cases of Raynaud's disease and in 6 cases in which Raynaud's phenomenon was associated with such vascular disturbances as acrosclerosis (2 cases), thromboangiitis obliterans (1 case), arteriosclerosis obliterans (1 case), livedo reticularis (1 case), and occupational occlusive disease of the arteries (1 case). As a control measure, the fingers and toes of the opposite extremities were anointed simultaneously with lanolin alone.

After inunction of the fingers with the glyceryl trinitrate ointment, there was an increase in the blood flow in the ipsilateral fore-

Table 1.—*Effect of Inunction of Fingers and Toes with 2 Per Cent Glyceryl Trinitrate in Lanolin on Blood Flow in Whole Forearm and Leg in Cases of Disturbances of Peripheral Circulation*

Case	Diagnosis	Extremity	Blood flow, cc. per 100 cc. of tissue					
			Digits treated with 2% glyceryl trinitrate in lanolin			Digits treated with lanolin		
			Before treatment	After treatment*	Change, %	Before treatment	After treatment*	Change, %
1	Raynaud's disease	Upper	3.1	4.0	+29	3.4	4.6	+35
		Lower	3.2	2.8	−12	3.1	3.9	+26
2	Raynaud's disease	Upper	6.1	9.1	+49	5.4	7.8	+44
		Lower	2.5	3.5	+40	3.1	3.4	+10
3	Raynaud's disease	Upper	2.3	3.6	+57	3.0	5.7	+90
		Lower	1.9	1.9	0	2.4	2.6	+8
4	Acrosclerosis with Raynaud's phenomenon	Upper	5.1	5.8	+14	6.7	6.5	−3
		Lower	3.5	5.2	+49	2.7	3.1	+15
5	Acrosclerosis with Raynaud's phenomenon	Upper	8.9	11.6	+30	7.3	9.6	+32
		Lower	3.5	5.6	+60	2.7	3.5	+30
6	Thromboangiitis obliterans with Raynaud's phenomenon	Upper	3.3	3.6	+9	5.2	7.2	+38
		Lower	2.8	3.3	+18	2.3	3.1	+35
7	Arteriosclerosis obliterans with Raynaud's phenomenon	Upper	5.9	8.5	+44	4.3	5.3	+23
		Lower	2.4	3.6	+50	1.9	2.3	+21
8	Livedo reticularis with Raynaud's phenomenon	Upper	4.6	4.9	+7	5.3	4.7	−11
		Lower	2.4	2.3	−4	1.8	2.1	+17
9	Occupational occlusive arterial disease with lower Raynaud's phenomenon	Upper	8.5	17.8	+109	7.7	18.8	+144
		Lower	2.3	5.2	+126	3.1	5.6	+81

* Maximum of 3 determinations.

arm in all of the 3 cases of Raynaud's disease (cases 1, 2 and 3). After inunction of the toes with this ointment, there was an increase in the blood flow in the ipsilateral leg in only one of these cases, namely, case 2. Inunction of the fingers and toes with lanolin alone was followed by an increase in the blood flow in the ipsilateral forearm and leg in all of these 3 cases.

In the 6 cases in which Raynaud's phenomenon was associated with such vascular disturbances as acrosclerosis, thromboangiitis obliterans, arteriosclerosis obliterans, livedo reticularis, and occupational disease of the arteries (cases 4 to 9 inclusive), the effects of the inunction on the blood flow were very similar to those observed in the 3 cases of Raynaud's disease (cases 1, 2 and 3).

In the case in which Raynaud's phenomenon was associated with thromboangiitis obliterans (case 6) and in the case in which this phenomenon was associated with arteriosclerosis obliterans (case 7), an increase in the blood flow in the forearm and leg was observed after inunction with the glyceryl trinitrate ointment and after inunction with lanolin alone. In this case, the pulse in the toes which were anointed with lanolin could not be obtained before the lanolin was applied, and marked ischemia of one toe was apparent. In all of the 9 cases in table 1, the respective increases which occurred in the blood flow in the forearm and leg after inunction with glyceryl trinitrate ointment and with lanolin may be attributed to systemic absorption of the glyceryl trinitrate.

TABLE 2.—*Effect of Inunction with 2 Per Cent Glyceryl Trinitrate in Lanolin on Skin Temperature of Fingers and Toes in Cases of Disturbances of Peripheral Circulation*

Case	Diagnosis	Digit	Temperature, degrees C.					
			Digits treated with 2% glyceryl trinitrate in lanolin			Digits treated with lanolin		
			Before treatment	After treatment*	Difference	Before treatment	After treatment*	Difference
1	Raynaud's disease	Finger	27.0	29.3	+2.3	26.6	27.3	+0.7
		Toe	26.4	27.2	+0.8	26.3	26.2	−0.1
2	Raynaud's disease	Finger	31.2	34.1	+2.9	29.5	34.2	+4.7
		Toe	24.1	28.2	+4.1	25.1	27.4	+2.3
3	Raynaud's disease	Finger	29.7	34.7	+5.0	34.7	35.7	+1.0
		Toe	25.1	26.3	+1.2	26.0	26.5	+0.5
4	Acrosclerosis with Raynaud's phenomenon	Finger	28.0	21.0	+3.0	30.4	33.1	+2.7
		Toe	25.6	29.2	+3.6	25.1	26.9	+1.8
5	Acrosclerosis with Raynaud's phenomenon	Finger	32.4	33.1	+0.7	30.5	32.1	+1.6
		Toe	27.4	30.4	+3.0	27.1	29.1	+2.0
6	Thromboangiitis obliterans with Raynaud's phenomenon	Finger	33.5	35.1	+1.6	34.0	35.1	+0.9
		Toe	27.1	28.2	+1.1	26.9	28.1	+1.2
7	Arteriosclerosis obliterans with Raynaud's phenomenon	Finger	34.7	34.8	+0.1	34.0	34.7	+0.3
		Toe	30.2	30.6	+0.4	27.0	27.1	+0.1
8	Livedo reticularis with Raynaud's phenomenon	Finger	32.2	31.0	−1.0	33.4	30.2	−3.2
		Toe	29.6	29.9	+0.3	30.2	28.6	−1.6
9	Occupational occlusive arterial disease with Raynaud's phenomenon	Finger	35.4	36.7	+1.3†	35.8	36.5	+0.7
		Toe	29.4	36.3	+6.9	29.9	35.2	+5.3

* Maximum of 3 determinations.

† The digits anointed with glyceryl trinitrate in lanolin had poor circulation owing to arterial occlusion while the digits anointed only with lanolin had normal circulation.

Table 2 shows the effect of inunction with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the skin temperature of the fingers and toes in the same group of cases (cases 1 to 9 inclusive) listed in table 1. The effects on the skin temperature were variable. In all but one of the cases (case 8) there was an increase in the skin temperature of the fingers and toes that were anointed with 2 per cent glyceryl trinitrate in lanolin. The increase, how-

ever, was small and insignificant in most instances. Similarly, there was an increase in the skin temperature in all but 3 instances in 2 cases (cases 1 and 8) after inunction of the fingers and toes with lanolin alone. In all but 2 of the cases (cases 2 and 5) the increase in the skin temperature was greater in the digits treated with the glyceryl trinitrate ointment than it was in the digits treated with lanolin alone.

Because of the probability that the use of a plethysmograph enclosing the entire forearm or leg might not indicate correctly the effects on the blood flow to the digits, we made additional studies by using a hand plethysmograph in 11 cases of Raynaud's disease and in 2 cases in which Raynaud's phenomenon was associated with such vascular disturbances as acrosclerosis (1 case) and chronic occlusive disease of the arteries (1 case). Table 3 shows the effects of inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the blood flow in the hand. In the 11 cases of Raynaud's disease (cases 12 to 22 inclusive), inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin was followed by an average increase of 176 per cent in the blood flow in the treated hand while inunction with lanolin alone was followed by an increase of 90 per cent in the blood flow of the treated hand. In all but one of these 11 cases (case 22), the increase in the blood flow in the hand was greater after inunction with the glyceryl trinitrate ointment than it was after inunction with lanolin alone.

In one case in which Raynaud's phenomenon was associated with acrosclerosis (case 10) and in another case in which this phenomenon was associated with chronic occlusive disease of the arteries (case 11), the increase in the blood flow in the hand was greater after inunction with the glyceryl trinitrate ointment than it was after inunction with lanolin alone.

Table 4 shows the effect of inunction of the fingers with 2 per cent glyceryl trinitrate in lanolin and with lanolin alone on the skin temperature of the treated digits in the same cases listed in table 3. The results recorded in table 4 are similar to those recorded in table 3. Inunction of the fingers with the glyceryl trinitrate ointment and with lanolin alone was followed by an increase in the skin temperature of the treated digits in all but 2 of the 11 cases of Raynaud's disease (cases 12 and 17) while

TABLE 3.—*Effect of Inunction of Fingers with 2 Per Cent Glyceryl Trinitrate in Lanolin on the Blood Flow in the Hand in Cases of Raynaud's Disease and Raynaud's Phenomenon*

Case	Diagnosis	Blood flow, cc. per 100 cc. of tissue					
		Fingers treated with 2% glyceryl trinitrate in lanolin			Fingers treated with lanolin		
		Before treatment	After treatment*	Change, %	Before treatment	After treatment*	Change, %
10	Acrosclerosis with Raynaud's phenomenon	3.0	7.3	+143	3.7	4.0	+8
11	Chronic occlusive arterial disease with Raynaud's phenomenon	8.2	21.9	+167	6.3	16.0	+154
12	Raynaud's disease	1.2	4.5	+275	2.0	2.0	0
13	Raynaud's disease	4.0	9.3	+133	3.3	6.0	+82
14	Raynaud's disease	6.9	12.3	+78	9.4	14.2	+51
15	Raynaud's disease	5.0	23.5	+370	6.5	16.0	+146
16	Raynaud's disease	7.4	16.3	+120	3.1	5.5	+77
17	Raynaud's disease	6.5	9.8	+51	7.4	8.6	+16
18	Raynaud's disease	3.3	7.3	+121	2.9	5.5	+90
19	Raynaud's disease	3.4	17.5	+415	4.3	21.8	+407
20	Raynaud's disease	3.2	8.8	+175	3.2	4.0	+25
21	Raynaud's disease	4.2	6.0	+43	8.2	9.7	+18
22	Raynaud's disease	5.5	8.4	+53	6.9	12.4	+80

* Maximum of 3 determinations.

inunction with lanolin alone was followed by an increase in the skin temperature in all but one of the 11 cases (case 12). The average increase in the skin temperature of the treated digits was 3.5 C. after inunction with the glyceryl trinitrate ointment and 2 C. after inunction with lanolin alone. Similar results were obtained in one case in which Raynaud's phenomenon was associated with acrosclerosis (case 10) and in another case in which this phenomenon was associated with chronic occlusive disease of the arteries (case 11).

TABLE 4.—*Effect of Inunction with 2 Per Cent Glyceryl Trinitrate in Lanolin on Skin Temperature of Fingers in Cases of Raynaud's Disease and Raynaud's Phenomenon*

Case	Diagnosis	Temperature, degrees C.					
		Fingers treated with 2% glyceryl trinitrate in lanolin			Fingers treated w th lanolin		
		Before treatment	After treatment*	Difference	Before treatment	After treatment*	Difference
10	Acrosclerosis with Raynaud's phenomenon	25.6	29.9	+4.3	25.5	28.0	+2.5
11	Chronic occlusive arterial disease with Raynaud's phenomenon	32.0	34.5	+2.5	33.1	34.7	+1.6
12	Raynaud's disease	26.6	26.5	−0.1	26.7	26.0	−0.7
13	Raynaud's disease	27.7	33.6	+5.9	27.7	28.1	+0.4
14	Raynaud's disease	32.4	35.4	+3.0	32.7	36.0	+3.3
15	Raynaud's disease	30.7	34.9	+4.2	30.0	34.2	+4.2
16	Raynaud's disease	33.4	35.6	+2.2	30.0	30.4	+0.4
17	Raynaud's disease	32.2	32.1	−0.1	33.1	33.3	+0.2
18	Raynaud's disease	31.0	33.1	+2.1	31.7	32.9	+1.2
19	Raynaud's disease	31.4	35.3	+3.9	30.1	35.2	+5.1
20	Raynaud's disease	31.2	33.6	+2.4	30.6	31.9	+1.3
21	Raynaud's disease	27.4	34.3	+6.9	31.9	34.4	+2.5
22	Raynaud's disease	27.8	34.4	+6.6	29.8	34.1	+4.3

* Maximum of 3 determinations.

The results of our study leave little doubt that the local application of 2 per cent glyceryl trinitrate in lanolin improves the circulation. The improvement was indicated by an increase in the blood flow and in the skin temperature in most instances, although the amount of the increase was variable. The increase in blood flow to the extremities treated with lanolin only was less in most instances than was the increase in the extremities treated with nitroglycerine ointment.

It appeared important to determine whether the act of rubbing or the systemic absorption of glyceryl trinitrate or both caused the apparent increase in blood flow and in the skin temperature. It had been noted that the improvement in circulation in the extremities to which lanolin alone had been applied invariably appeared in the final stage of the observation. No very significant changes were noted in the blood flow or in the skin temperature in cases in which one hand was rubbed with lanolin ointment alone while the other hand remained untreated. Therefore, it seemed to us that, on the basis of this evidence, whatever increase occurred in the circulation of the extremities treated with lanolin alone when the opposite part was rubbed with glyceryl trinitrate ointment could not be adequately explained on the basis of rubbing alone but was also attributable to the systemic absorption of glyceryl trinitrate. This was further substantiated by the fact that nitrite headache commonly occurred after inunction with the glyceryl trinitrate ointment.

A careful study of our records indicates that the following conclusions are valid. The local application of glyceryl trinitrate in lanolin to the digits of an extremity usually causes an improvement in the circulation of the extremity. There is usually improvement in the circulation of the companion extremity, which,

however, is ordinarily of smaller magnitude and is due to the absorption of glyceryl trinitrate into the general circulation.

Action of Other Vasodilating Drugs

In order to determine whether the local application of other vasodilating drugs would produce the same effects as those produced by similar application of glyceryl trinitrate in cases of Raynaud's disease, we applied ointments containing 10 per cent of Priscoline (2-benzylimidazoline hydrochloride), 5 per cent of nicotinic acid, 3.5 per cent of Mecholyl chloride, 0.9 per cent of histamine diphosphate and 20 per cent of Etamon chloride (tetraethylammonium chloride), respectively, in a base of equal parts of petrolatum and lanolin. The method used in this part of our study was the same as that used in our investigation of glyceryl trinitrate. A hand plethysmograph was used to determine the effects of these drugs on the blood flow. Local application of these drugs failed to produce any significant alteration in the blood flow or in the skin temperature in cases of Raynaud's disease.

TABLE 5.—*Clinical Results of Topical Application of 2 Per Cent Glyceryl Trinitrate in Lanolin in Cases of Raynaud's Disease and Raynaud's Phenomenon*

Diagnosis	Cases	Improvement			
		Great	Moderate	Slight	None
Raynaud's disease	15	3	5	2	5
Acrosclerosis with Raynaud's phenomenon	7		1	2	4
Occupational occlusive arterial disease with Raynaud's phenomenon	2	1	1		
Thromboangiitis obliterans with Raynaud's phenomenon	1				1

CLINICAL OBSERVATIONS

Although the results of the pharmacologic part of our study seem to be of some importance, our main objective was to determine whether repeated local application of 2 per cent glyceryl trinitrate in lanolin would prevent the episodes of discoloration of the skin which are characteristic of Raynaud's disease and Raynaud's phenomenon. In order to obtain this information, the ointment was applied locally in 25 cases of Raynaud's disease or Raynaud's phenomenon. In all of these cases, the untreated hand was gloved while the ointment was being applied to the opposite hand. The pertinent data in 6 cases will be summarized briefly.

Case 28. A man, aged 24 years, had had Raynaud's phenomenon of the second finger of the right hand for two weeks, apparently as a result of the use of a vibrating tool. Arteriography disclosed evidence of occlusive arterial disease. After glyceryl trinitrate ointment had been applied for three months, the affected finger appeared warmer and less numb than it had been previously. The color improved, but slight pallor occurred on cold days.

Case 30. A woman, aged 53 years, had noted sensitiveness of her hands and feet to cold since childhood. She had had episodes of discoloration of the fingers, characteristic of Raynaud's disease, for 10 years. Sympathectomy had been performed four years previously but had not produced any benefit. Application of glyceryl trinitrate ointment four times daily for seven weeks did not have any effect on the episodes of discoloration.

Case 38. A woman, aged 38 years, had had advanced acrosclerosis of the hands, forearms, neck, face, and esophagus for six years. Examination disclosed bilateral trophic changes of the nails and Raynaud's phenomenon of the fingers. She applied about 1 Gm. of glyceryl trinitrate ointment to the right hand four times daily while the contralateral hand was gloved. After seven days of inunction, no clinical improvement in her hands was noted.

Case 42. A man, aged 49 years, who did not smoke, had had episodes of pallor and rubor in the third and fourth fingers of his left hand upon exposure to cold or excitement for eight months. In addition, he had had three episodes of thrombophlebitis in his legs within the past four years, numerous instances of nocturnal cramps in his legs and often had had a dull ache associated with pallor in his fingers. Examination disclosed obliteration of pulsation in both ulnar arteries. The result of Allen's test was positive. Pulsation was normal in the other peripheral arteries. Examination disclosed pallor, grade 2, of the right hand and pallor, grade 1, of the left hand upon elevation. The diagnosis was chronic occlusive arterial disease (probably thromboangiitis obliterans) associated with Raynaud's phenomenon. The patient applied glyceryl trinitrate ointment to his left hand four times daily for several days but he was unable to notice any improvement.

Case 46. A housewife, aged 28 years, had had epi-

sodes of discoloration of both hands and all of the toes for one year. The episodes had tended to occur after exposure to cold but they also had occurred without any apparent cause. In the course of the episodes, the involved parts first had become white, then red, and finally blue. The diagnosis was Raynaud's disease. The patient also had hyperhidrosis, and the history was suggestive of hyperventilation and chronic nervous exhaustion. Pulsation was normal in the peripheral arteries, and there was no evidence of acrosclerosis or any contributing vascular disturbance. After the patient had applied glyceryl trinitrate ointment to the right hand, the episodes of discoloration disappeared in this hand.

Case 47. A retired salesman, aged 66 years, had become fatigued easily, had become unusually dyspneic on exertion, and had had episodes of discoloration of his fingers and feet for ten years. The episodes of discoloration had been characteristic of Raynaud's disease. The blood pressure was 180/106. Examination disclosed benign hypertrophy of the prostate gland and some narrowing and sclerosis of the retinal arteries. The value for the blood urea was 52 mg. per 100 cc. The diagnosis was essential hypertension, mild hypertensive heart disease and Raynaud's disease. After the patient had applied glyceryl trinitrate ointment to his hands and feet for three days, his hands became warm for the first time in 10 years and failed to become discolored on exposure to cold.

Summary

We have investigated the effect of repeated inunction with 2 per cent glyceryl trinitrate in lanolin on the blood flow and skin temperature of the extremities in 14 cases of Raynaud's disease and in 8 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis (3 cases), chronic occlusive disease of the arteries (3 cases), occupational disease of the arteries (1 case) and livedo reticularis (1 case). The inunction almost invariably caused an increase in the blood flow and in the skin temperature of the digits in the 14 cases of Raynaud's disease. The increase which occurred in the circulation of the untreated extremity was attributed to the systemic absorption of glyceryl trinitrate. In the 8 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis, chronic occlusive disease of the arteries, occupational disease of the arteries and livedo reticularis, the inunction produced an inconsistent increase in the blood flow and in the skin temperature of the extremity. Applications of lanolin alone and of 10 per cent Priscoline (2-benzylimidazoline hydrochloride), 5 per cent nicotinic acid, 3.5 per cent Mecholyl chloride, 0.9 per cent histamine diphosphate and 20 per cent Etamon chloride (tetraethylammonium chloride), respectively, in a base of equal parts of petrolatum and lanolin did not produce any significant increase in the circulation in the cases of Raynaud's disease in which they were used.

After we had completed the pharmacologic phase of our study, we investigated the therapeutic effect of repeated inunction with the glyceryl trinitrate ointment on the episodes of discoloration which are characteristic of Raynaud's disease and Raynaud's phenomenon. The ointment was applied in 15 cases of Raynaud's disease and in 10 cases in which Raynaud's phenomenon was associated with such vascular diseases as acrosclerosis (7 cases), occupational occlusive disease of the arteries (2 cases), and thromboangiitis obliterans (1 case). In the 15 cases of Raynaud's disease, the results were variable. Great improvement occurred in 3 cases, moderate improvement occurred in 5 cases, but little if any improvement was observed in the 7 remaining cases. The results also were variable in the 7 cases in which Raynaud's phenomenon was associated with acrosclerosis. Moderate improvement occurred in 1 case, but little if any improvement was observed in the 6 remaining cases. In one of the cases in which Raynaud's phenomenon was associated with occupational occlusive disease of the arteries, great improvement occurred; in the other case, only moderate improvement was observed. No improvement occurred in the case in which Raynaud's phenomenon was associated with thromboangiitis obliterans (table 5).

In the cases of Raynaud's disease, as well as in the cases of Raynaud's phenomenon, the improvement produced by glyceryl trinitrate ointment was only temporary. This treatment, therefore, is only palliative.

In practically all of the 25 cases, a transient dull headache developed within from a half hour to two hours after the ointment had been applied. After the ointment had been applied for several days, the headache usually disap-

peared. With the exception of the headache, we have not observed any untoward effect of application of the ointment.

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Extensive Calcification of the Myocardium

Report of a Case

By A. Carlton Ernstene, M.D., and John B. Hazard, M.D.

An unusual case of extensive calcification of the myocardium in a 25 year old woman is presented. Presumably it was the result of an earlier severe toxic or septic myocarditis.

PATHOLOGIC deposits of calcium may occur in valve leaflets and valve rings, in the pericardial scar of chronic constrictive pericarditis, and in the myocardium. In each of these regions, the areas of calcification may be demonstrated by appropriately taken roentgenograms. Their detection often is of considerable diagnostic importance. The most common cause of calcification in the myocardium is myocardial infarction, the calcium being deposited during the process of healing of the infarct. In addition, myocardial calcification may occur as a complication of hyperparathyroidism[1] and as a result of focal toxic or inflammatory myocardial necrosis.[2–5] Areas of bone formation may also be present. A review of the literature has been presented recently by Finestone and Geschickter.[6]

Report of Case

A white, single woman, aged 25 years, was admitted to the hospital on Nov. 7, 1946 because of progressive dyspnea of two years' duration. At the age of 9 years, she had had scarlet fever of such severity that she was out of school for one year. No cardiac or renal symptoms could be recalled. Four years before admission she had suffered from pneumonia and had been kept in bed for one month. Two years later there had been an acute upper respiratory infection, and since that time she had had noticeable shortness of breath on exertion. In January, 1946, cough and increasing dyspnea necessitated a 4 weeks' period of rest in bed, but the patient was then able to return to work as a clerk until June. From June onward, dyspnea and cough progressively became more severe, and approximately 10 days before admission a sudden further increase in these symptoms was accompanied by the first appearance of cyanosis and swelling of the face, neck, and abdomen.

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Physical examination revealed a well developed, well nourished young woman with severe orthopnea, cyanosis of the lips and nail beds, and moderate distention of the jugular veins. The temperature was normal, the heart rate 120 per minute, and the blood pressure 80 mm. systolic, and 60 mm. diastolic. There was slight puffiness of the face. Signs of fluid were present over the lower half of the right thorax posteriorly, and there were numerous moist rales above this level as well as over the lower lobe of the left lung. The heart was greatly enlarged to the left; its rhythm was regular except for an occasional premature beat, and no murmurs were present. All heart sounds were of average intensity. The liver extended 14 cm. below the costal margin in the right midclavicular line and was moderately tender. The edge of the spleen could be felt 4 cm. below the costal margin. There was no peripheral edema.

The urine had a specific gravity of 1.020 and contained 3 plus albumin and an occasional hyaline or granular cast. The red blood cell count was 6,140,000 per cu. mm., and the hemoglobin content was 16.0 Gm. The leukocyte count was 12,000 per cu. mm. The Wassermann reaction of the blood was negative.

An electrocardiogram showed sinus tachycardia with a rate of 116 per minute. The P waves were notched in lead I. The P-R intervals were within normal limits but the duration of the QRS complexes was increased to 0.11 second. There was slurring of QRS in leads I and II, and right axis deviation was present. The T waves were inverted in leads II and III.

Portable anteroposterior roentgenograms of the thorax were of poor quality but revealed opacity of the right thorax with slight displacement of the trachea and mediastinum to the left. Extensive areas of increased density, suggestive of calcium deposits, were present within the area of a much enlarged cardiac shadow.

Digitoxin, mercurial diuretics, a low sodium diet, the administration of oxygen, and right thoracentesis with the removal of 650 cc. of clear, straw colored fluid resulted in only slight and temporary improvement. On the twelfth day in the hospital the patient suddenly developed acute pulmonary edema and died.

Postmortem examination revealed the heart to be

greatly enlarged and to weigh 950 Gm. There were numerous irregular, white projections of calcification

FIG. 1. Epicardial surface of the left ventricle and left auricle. Numerous irregular projections of calcium are seen.

FIG. 2. Illustrating the extensive irregular calcification in the wall of the left ventricle and left auricle.

over the epicardial surface of the left auricle and ventricle (fig. 1). The right heart appeared normal externally except for dilatation of the auricle. The left auricle and ventricle were opened only with difficulty, and cut sections of their walls revealed extremely extensive, irregular depositions of calcium (fig. 2). Only a small area on the posterior wall of the ventricle near the septum was not affected. The interventricular septum showed similar massive involvement but the right auricle and right ventricle were affected to a much lesser degree (fig. 3). Multiple calcific excrescences were present on the endocardial surface of the left auricle, left ventricle and pulmonary conus, ranging up to 4 mm. in diameter and 5 mm. in elevation. The extent and degree of the calcification in the heart as a whole was well demon

FIG. 3. The right chambers of the heart have been opened to demonstrate the much lesser extent of calcification in the wall of the right ventricle.

strated by roentgenograms of the fresh, isolated organ (fig. 4).

The heart valves were normal. There were two small mural thrombi in the left auricle and a single thrombus of larger size was present near the apex of the left ventricle. The coronary arteries were normal. There were 70 cc. of straw colored fluid in the pericardial sac but the pericardium was normal except for two small, irregular roughened areas in the posterior portion opposite one of the larger calcific protuberances. No adhesions were present. The aorta appeared somewhat small in diameter throughout its entire length but was otherwise normal.

Examination of the abdominal viscera and lungs revealed severe chronic passive congestion. Right hydrothorax was present, and the lower lobe of the

FIG. 4. Roentgenogram of the fresh, isolated heart to demonstrate the extent and degree of calcification of the myocardium.

right lung showed compression atelectasis and a large area of recent infarction.

Microscopic examination of the myocardium revealed extensive areas of calcification within broad zones of cicatrization (fig. 5, *left*). Some of the calcific masses included islands of bone formation (fig. 5, *right*). Muscle fibers marginal to regions of fibrosis were to a considerable extent individually separated by fibrous tissue continuous with the partly calcified cicatrices. In addition, there were focal areas of myocardial scarring without accompanying calcific material. No areas of calcification were present in sections of the lungs and kidneys.

DISCUSSION

It is of interest that the calcium deposits in the cardiac area had been recognized by roentgenologic examination before the patient's admission to the hospital and the possibility of chronic constrictive pericarditis with pericardial calcification had been suggested. The patient's general condition after admission precluded additional detailed roentgenologic and fluoroscopic studies, and the significance of the calcium deposits was not correctly assessed prior to the patient's death. It was believed,

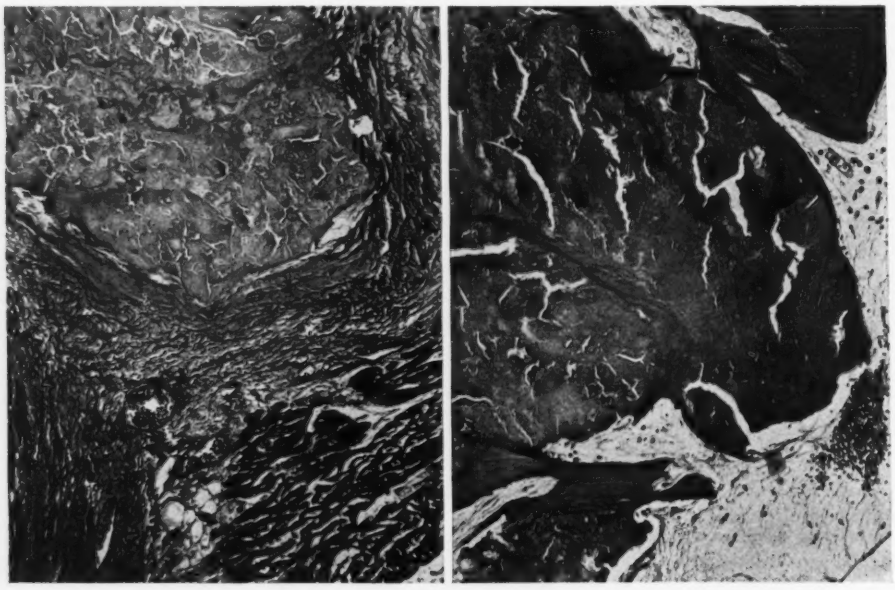

FIG. 5 *Left*. Histologic section of the left ventricle myocardium showing an extensive area of calcification surrounded by a broad zone of dense connective tissue. ×70. *Right*. Wall of left ventricle showing areas of bone formation in a large calcific mass. ×100.

however, that the great enlargement of the heart was sufficient evidence to exclude chronic constrictive pericarditis as the cause of the illness. In chronic constrictive pericarditis the heart is surrounded by a firm, vise-like scar which interferes with diastolic relaxation of the ventricles and prevents hypertrophy and dilatation. Roentgenograms show the heart shadow to be of normal size or at the most only slightly enlarged.

The extensive myocardial calcification in the present case probably resulted from a severe toxic or septic myocarditis but the reason for the predominant involvement of the left auricle and ventricle and the interventricular septum is not known. The patient had experienced at least three illnesses that might have been attended by acute myocarditis. The first of these was severe scarlet fever 16 years before her admission to the hospital, the second was pneumonia 4 years before admission, and the third was an acute upper respiratory infection 2 years before the terminal illness. No decision can be made as to whether any of these actually was an etiologic factor. The most severe infection apparently was the scarlet fever but it would seem most unusual for a patient to live for 16 years after having experienced such severe damage to the myocardium.

Summary

Extensive calcification of the myocardium, involving predominantly the left auricle and ventricle and the interventricular septum, was found in a 25 year old woman who died of congestive heart failure. The etiology of the condition was not determined but it is probable that the deposition of calcium occurred during the healing phase of an earlier severe toxic or septic myocarditis.

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Digital Vascular Resistance in Normal, Polycythemic and Hypertensive States

By MILTON MENDLOWITZ, M.D.

The relationship between blood pressure and flow in the digital circulation has been found to be rectilinear. This makes it possible from a single pressure-flow determination to measure (1) digital vascular configuration volume index, (2) initial digital arterial caliber, (3) resistance in dyne second/cm.^{5}, (4) resistance in dynes and (5) resistance in dynes/cm.^{2}. The normal variations in these values and the deviations from the normal found in hypertension and polycythemia are presented.

PERIPHERAL resistance has in the past been measured by dividing pressure by flow and multiplying this value by a constant. This determination includes the so-called viscosity factor and assumes that with unchanged resistance the relationship between pressure and flow with varying pressures is rectilinear. It has, however, been demonstrated by many workers[1–4] that especially in small blood vessels this relationship may not be a straight line. It has also been found that apparent viscosity may not be a constant but may change with changes in velocity, in caliber of the perfused vessels and in the nature of the perfusate.[5] It was our purpose to study the pressure-flow relationship in the digital circulation and to attempt separation of the various factors in the peripheral resistance in order to compare the abnormal with the normal circulation.

If the vascular bed of a dog's leg is perfused with Ringer's solution or plasma, the relationship between pressure and flow is rectilinear.[5] If venous pressure is subtracted from arterial pressure in the calculations, a measure neglected by earlier workers,[5] the straight line intercepts the pressure axis at or near zero. Poiseuille's law[6] is then applicable, the formula being

$$Q = \frac{P\pi r^4}{8l\eta} \qquad (1)$$

in which Q is the volume flow in cm.^{3}/second, P the mean arterial pressure minus the venous pressure converted into dynes/cm.^{2}, r the radius of the tube in cm., l the length of the tube in cm. and η the viscosity in poises (dyne second/cm.^{2}). If r, l, and η are fixed, the only variables are P and Q and the formula becomes the familiar $Q = Pk$ in which k is a constant. This is clearly a rectilinear equation.

When blood is used as the perfusing fluid the relationship between P and Q has been interpreted by different workers to be rectilinear with a shifting intercept on the pressure axis,[5] hyperbolic, approaching an asymptote,[4] or logarithmic.[1, 3] There are several possible factors involved in this deviation from the poiseuilleian straight line. Increasing pressure may distend blood vessels progressively or open new capillaries especially at low velocity rates.[1] With maximum vasodilatation, however, the effect of pressure on the vessels becomes minimal. What is more, curves similar to those seen in vivo may be obtained by perfusing glass tubes of appropriate diameter.[7] Changes in the physical elasticity or compressibility of the cells and plasma are too small to account for the effects observed at low pressures.[8] The lower portion of the curve may, however, be affected by changes in alignment and distribution of cells and possibly by changes in their shapes at lower pressures as compared with higher pres-

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sures. This is sometimes referred to as plasticity.[3] The slope of the upper portion of the curve is modified at vascular resistances prevailing in the peripheral circulation by the Fåhraeus phenomenon.[9] This represents a decrease in apparent viscosity with decreasing tube caliber below a critical radius. This is caused by proportionate increase in the peripheral zone of plasma, which is less viscous than blood, the cells being crowded into the center of the stream. It is this effect which creates considerable discrepancy between viscosity determined in vivo as against in vitro observations.[5] It has also been shown, however, that increasing vasoconstriction in the hind limb of the dog increases apparent viscosity.[2] Because of the simultaneously increased intercept of the major pressure-flow slope on the pressure axis, this increase in viscosity is greatest at very low rates of flow. At such low rates of flow, moreover, ischemia can cause capillary dilatation with variable changes in diffusion from capillaries to tissues which may modify pressure-flow curves by changing the red cell and plasma protein concentration of the blood.[1] Such changes in diffusion are theoretically possible at higher flow rates but are probably unimportant in the terminal digit where most of the flow is through arteriovenous anastomoses.[10]

Logarithmic formulas for the pressure-flow relationship have been fitted to empiric data and have been found to be $Q = aP^{k}$ [3] or $Q = (P/m)^{n}$ [1] in which a and k or m and n are constants. In such a formula the logarithmic function k or n is the plasticity factor and a or m the variables of Poiseuille's law, r, l and η together with the Fåhraeus phenomenon factor. The exact relationship of these factors has not yet been worked out physically although Lamport[11] has recently presented a logarithmic formula incorporating the factor of caliber. The constant, k, has been found to vary from 1.4 to 1.8 in animal perfusion experiments.[3] It must be remembered, however, that these formulas are derived from data obtained by the perfusion of vascular beds in which the preponderance of flow is through capillaries. In the human digital circulation in which sympathetic tone is released the preponderance of flow is through arteriovenous anastomoses. It therefore becomes necessary to determine the character of the pressure-flow curve in the human digital circulation to see if any difference can be detected between such curves and those obtained in animals and also to see if these pressure-flow relationships can be used to analyze digital vascular resistance.

To this end, studies were made after stabilization of the circulation by indirect heating, on a normal subject, on a patient with severe polycythemia vera, and on several patients with hypertension. Pressure-flow relationships at various digital arterial pressures were obtained by graded occlusion of the brachial artery. A blood pressure cuff could not be used because it introduced the factor of variable and progressive increase in venous pressure. A clamp was therefore devised that would produce a given degree of compression of the brachial artery without compressing the veins (fig. 1).

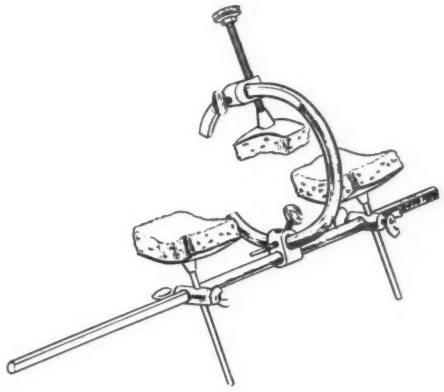

FIG. 1. Arterial compression clamp

That no significant increase in venous pressure occurred after compressing the brachial artery with this clamp was confirmed repeatedly by direct and indirect venous pressure determination. Direct measurement of brachial systolic and diastolic and planimetric mean pressures with a strain-gage manometer in several cases showed that the arithmetic mean corresponded fairly well with the true mean or was slightly higher. This relationship changed

very little if at all with brachial artery compression. What is more such compression produced no change in the erythrocyte concentration and hence viscosity of the perfusing arterial blood.

One possible source of error was the subtraction of 6 mm. Hg from the mean arterial pressure as average venous pressure. With decreasing digital arterial pressure the digital venous pressure might well fall. What is more the venous pressure in veins draining arteriovenous anastomoses might be somewhat higher than in those draining capillaries. Also, the venous pressure might act over a wider cross-

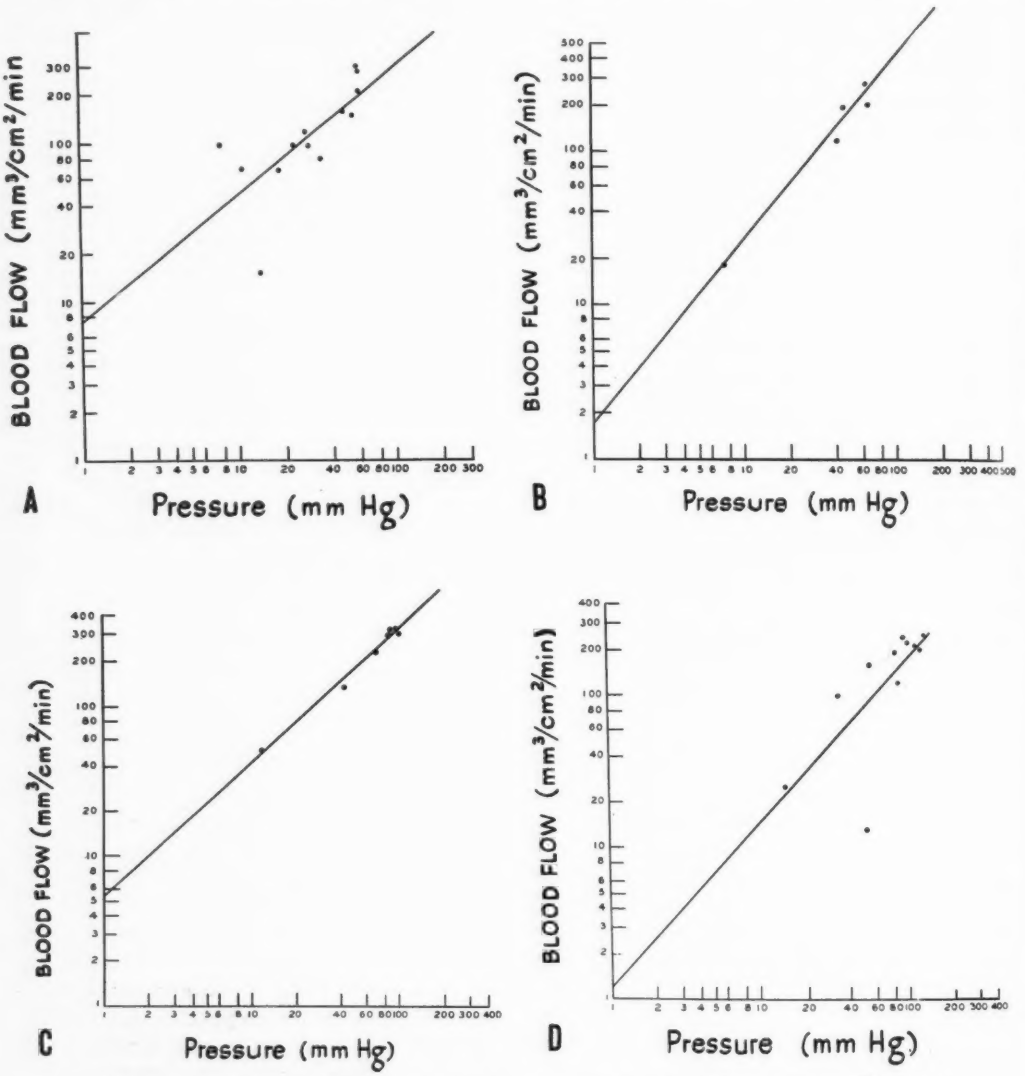

FIG. 2. Logarithmic pressure-flow relationships. *A*. Normal (M.M.): $Q = 7.491P^{0.7854}$. *B*. Polycythemia (M.K.): $Q = 1.678P^{1.1729}$. *C*. Mild essential hypertension (M.G.): $Q = 5.358P^{0.8810}$. *D*. Severe essential hypertension (A.B.): $Q = 1.155P^{1.0517}$.

sectional area than the arterial pressure which would create an error in estimating resistance in dynes (see below). These factors, however, appeared to be small enough to be negligible.

The validity of the technic for measuring blood flow was exhaustively established elsewhere.[12] Repeated pressure-flow determinations at heart level after maximal vasodilatation by indirect heating were made on different days in the same subject. It had been demonstrated that in any given individual this relationship was nearly identical from day to day.[12] Only those experiments were accepted in which the brachial pressure from day to day was stable and in which the digital pressures before and after the flow observations remained unchanged. That release of sympathetic nerve tone could be satisfactorily effected in the upper extremity by indirect heating was demonstrated by Arnott and Macfie.[13]

When our results were plotted by the method of the least squares[14] on logarithmic paper, using the formula, $Q = aP^k$, k was found to vary from 0.8 to 1.2 and not from 1.4 to 1.8 as had been found in animal experiments.[1, 3] Typical graphs are presented in figure 2. It is clear that when k is 1 or nearly 1 we are dealing again with a linear rather than a logarithmic relationship. The reason for the discrepancy between our studies and animal perfusion experiments probably lies in the fact that in the fingertip flow through arteriovenous anastomoses predominates over that through capillaries.

The results of our observations in normal, polycythemic and hypertensive subjects were hence plotted on cartesian coördinates (fig. 3). Since the rectilinear fit was as good as the logarithmic, the least squares method[14] was employed to determine straight line regressions. The intercepts of these lines hovered around zero. The deviations of the points from the pressure-flow lines were due to slight fluctuations in sympathetic nerve tone, to such errors as are inherent in the method, as well as to the fact that arithmetic and true mean pressures do not always coincide. The return of the pressure-flow ratio to normal in the bled polycythemic patient was nicely demonstrated. Consideration of probable error, however, indicated that the exact intercepts on the pressure axis could not be accurately determined from these lines, especially in hypertension, and could be considered to be 0 ± 10 mm. Hg.

If these observations are valid and the error involved in disregarding the intercepts on the pressure axis is sufficiently small, it becomes possible to apply Poiseuille's law to the digital circulation. In formula (1), η represents the viscosity of the blood. Whittaker and Winton[5] showed in animal perfusion experiments that normal intravascular blood viscosity is approximately 2.2 times that of Ringer's solution at a temperature of 37 C. The changes in viscosity, moreover, with varying erythrocyte concentration demonstrated by these workers in animals were reproduced in the human digital circulation.[15] The viscosity of water or Ringer's solution at 37 C. is 0.0069; that of blood is 0.015 poises. There is an insignificant error involved here because the average temperature of the blood in the fingertip is 33 to 34 rather than 37 C. The increase in apparent viscosity with vasoconstriction described by Pappenheimer and Maes[2] in animal perfusion experiments was due chiefly to the increasing intercept of the pressure-flow slope on the pressure axis. Since such a shift is minimal in the digital circulation, if it occurs at all, the apparent viscosity can fairly safely be assumed to be 2.2 times that of water or Ringer's solution. It still remains necessary to demonstrate this relationship by perfusion experiments on amputated human extremities.

The only remaining unknowns in the equation are length and caliber. These two factors together represent the physical configuration of the digital blood vessels. Thus, transposing in equation (1)

$$\frac{\pi r^4}{8l} = \frac{Q\eta}{P} \qquad (2)$$

The vascular configuration volume index is represented by $\frac{\pi r^4}{8l}$. Thus, in a typical calculation, if the arithmetic mean digital arterial pressure minus venous pressure is 52 mm. Hg and the flow 0.0047 cc./second/cm.^{2} of skin, 5.2 cm. multiplied by 13.6 (specific gravity of mercury) and by 980 cm./second^2 (acceleration

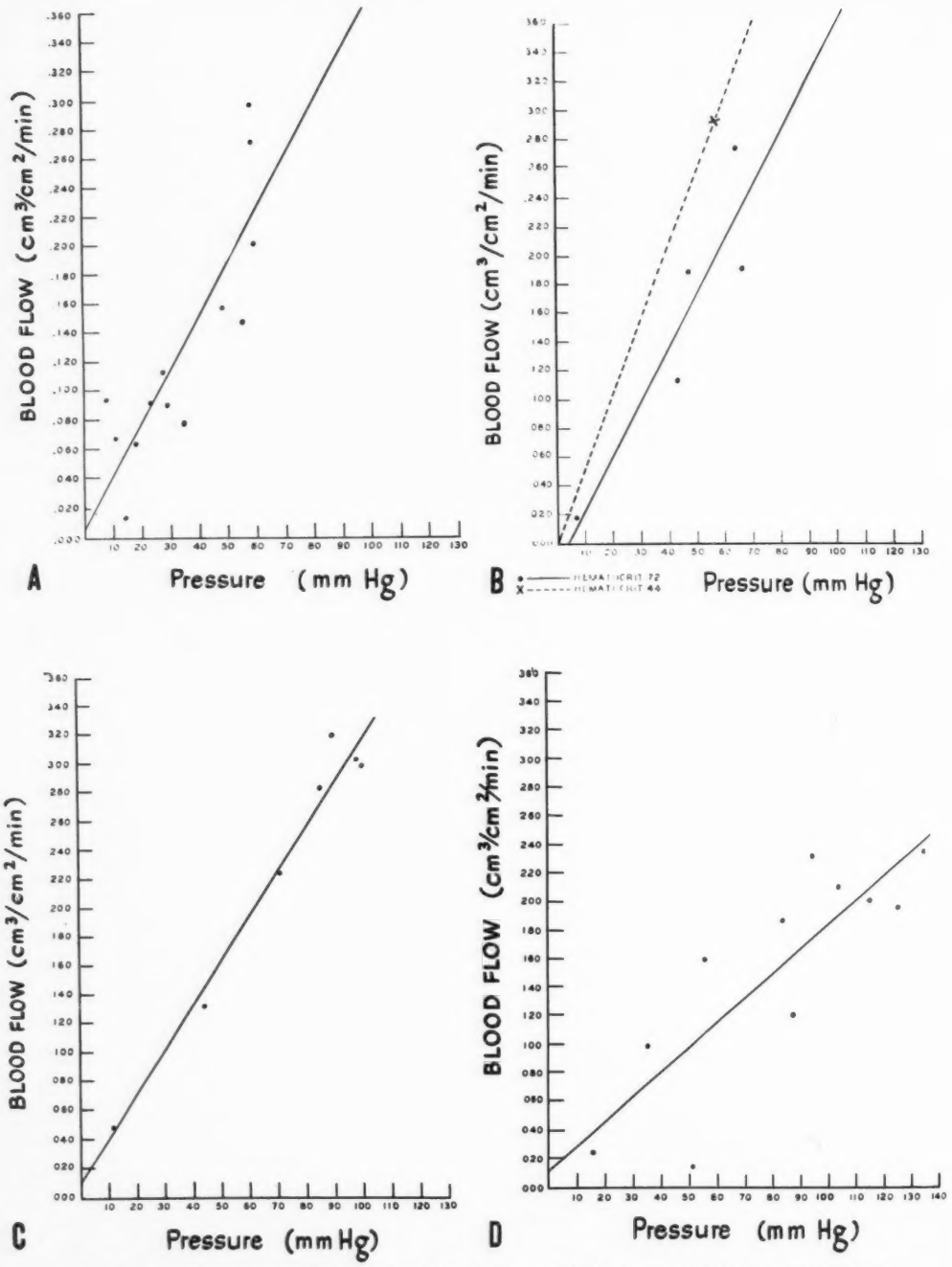

FIG. 3. Cartesian pressure-flow relationships. *A*. Normal (M.M.): $Q = 0.006846 + 0.003545P$. *B*. Polycythemia (M.K.): $Q = -0.013384 + 0.003705P$. *C*. Mild essential hypertension (M.G.): $Q = 0.00974 + 0.00307P$. *D*. Severe essential hypertension (A.B.): $Q = 0.011805 + 0.001706P$.

of gravity) equals 69306 dynes/cm.^{2}. η for normal blood is 0.015 dyne second/cm.^{2}. Hence, the vascular configuration volume index is

$$\frac{\frac{0.0047\ cm.^3}{sec.} \cdot \frac{0.015\ dyne\ sec.}{cm.^2}}{\frac{69306\ dynes}{cm.^2}} = 0.000000001010\ cm.^3$$

or 1010 cubic microns. Calculations of this index based on 34 normal subjects, 25 cases of essential hypertension, and 6 cases of malignant hypertension are presented in table 1. Calculations in a typical case of polycythemia, before and after repeated phlebotomy, are also presented in table 1. These results are representative of those calculated in 7 other cases of polycythemia. The data on some of these cases have already been published.[15, 16]

Separation of the factor of length from that of caliber is impossible in an irregularly branching system. Such separation can, however, be effected theoretically as follows: If it is assumed that Poiseuille's law applies to the systemic circulation as a whole,* the number of dynes of force at the sinuses of Valsalva would be represented by pressure in dynes/cm.^{2} multiplied by the aortic cross sectional area in

TABLE 1.—*Dimensions and Resistance of the Digital Vascular Bed*

Determination	Normal Range	Essential Hypertensive Range	Malignant Hypertensive Range	Polycythemia (M.K.)	
				Hematocrit 72%	Postphlebotomy Hematocrit 44%
Digital Vascular Volume Index/cm.^{2} of skin in cubic microns	1010–653	653–308	308–177	1177	946
Estimated length factor for one digital artery in cm. assuming average radius of 0.03 cm. and and adjusting value to average size fingertip	55.6	55.6	55.6	55.6	55.6
Initial caliber of a single digital artery (in cm. of radius) adjusted to average size fingertip	0.031–0.028	0.028–0.023	0.023–0.020	0.033	0.031
Resistance in dyne sec./cm.^{5} of a vascular bed perfused by a single digital artery (adjusting value to average size fingertip)	2,287,000–3,420,800	3,420,800–7,219,300	7,219,300–12,568,700	3,275,200	2,343,600
Resistance in dynes in a vascular bed perfused by a single digital artery (adjusting value to average size fingertip)	235–301	301–406	286–357	320	230
Resistance in dynes/cm.^{2} of cross-sectional area in a vascular bed perfused by a single digital artery (adjusting value to average size fingertip)	69,306–111,955	111,955–211,915	203,918–226,576	95,962	76,636

multiplied by the aortic cross sectional area in

* The plasticity factor modifies Poiseuille's law in the systemic circulation and the figures are inaccurate to that extent.[3]

cm.^{2}. If the cross sectional area as estimated roentgenographically is approximately 13 cm.^{2}, at a flow of 80 cm.^{3}/second and a mean pressure of 100 mm. Hg, a theoretic length factor can be calculated from equation (1) to be about 7 kilometers. This means that if the aorta were a uniform bore tube 7 kilometers long it would offer the same resistance as is offered by the entire systemic arterial tree, provided the viscosity of the blood were kept unchanged. It is also very probable that this length factor does not change much for any given vascular bed. Hence, if a length factor is established for a vascular bed in this way, the initial cross sectional area can be calculated back from the formula and its normal range of variation estimated.

The same process may be applied to the two digital arteries where Poiseuille's law does apply. Roentgenograms of these arteries in preliminary observations reveal an approximate initial diameter after vasodilatation of 0.06 cm. each as they enter the terminal segment of the finger, and the length factor in each entire digital circulation can be calculated to be approximately 55.6 cm. This means that if each digital artery were a uniform horizontal tube 55.6 cm. long it would offer a resistance comparable to that offered by the entire digital vascular bed supplied by that artery, provided the apparent viscosity remained unchanged. Both digital arteries are assumed to be equal in caliber and since caliber varies with the surface area perfused, a size factor, average surface/actual surface, has been incorporated in the calculation. The variations in caliber presented in table 1 may be modified when more extensive radiographic data on digital arteries in the vasodilated state become available.

To calculate resistance, formula (1) may be rearranged as follows:

$$\frac{P}{Q} = \frac{8l\eta}{\pi r^4} \tag{3}$$

Since P is expressed in dynes/cm.^{2} and Q in cm.^{3}/second, P/Q is expressed in dyne second/cm.^{5}. This method was introduced by Böger and Wezler[16] and is commonly used to measure peripheral resistance. When such resistance is calculated for the human systemic circulation as a whole[18] it is 539 to 1130 dyne second/cm.^{5}. For the rabbit it varies from 11,670 to 12,590[19] and for the vascular bed of a single digital artery in the normal fingertip from 2,287,000 to 3,420,800 dyne second/cm.^{5}. The normal and abnormal variations in digital vascular resistance calculated in this way are presented in table 1. Superficially it seems incredible that the resistance of systemic vessels in a rabbit, or in a fingertip, should be so much greater than the resistance of the entire human systemic circulation unless one remembers that the expression dyne second/cm.^{5} measures resistance in dynes per *unit* of blood flow and per *unit* of cross sectional area. It is therefore relative to the actual blood flow and actual cross sectional area.

The resistance in dynes can only be measured by multiplying the resistance in dyne second/cm.^{5} by the actual blood flow and cross sectional area. Thus if equation (3) is converted into physical units,

$$\frac{dynes/cm.^2}{cm.^3/second} = \frac{cm.\cdot dyne\cdot second/cm.^2}{cm.^4}$$

$$or \tag{4}$$

$$\frac{dyne\cdot second}{cm.^5} = \frac{dyne\cdot second}{cm.^5}$$

Multiplying both sides of the equation by the actual Q in cm.^{3}/second and the actual cross sectional area in cm.^{2}, we have

$$\frac{dyne\cdot second}{cm.^5}\cdot\frac{cm.^3}{second}\cdot cm.^2 = \frac{dyne\cdot second}{cm^5}\cdot\frac{cm.^3}{second}\cdot cm.^2$$

$$or\ dynes = dynes$$

Thus the force in dynes exerted by the pressure acting over the initial cross sectional area is equal to the resistance in dynes provided the flow is constant. In a system in dynamic equilibrium force and opposing resistance in dynes must be exactly equal. Such resistance is the resultant of the frictional forces in the blood stream acting in a direction opposite to that of pressure. To calculate force and hence resistance in dynes, it can be seen from equation (4) that the pressure in dynes/cm.^{2} may simply be multiplied by the calculated initial digital arterial cross sectional area in cm.^{2}, the flow factor being cancelled.

It is to be noted that resistance in dynes varies directly with pressure and directly with cross sectional area. Since the cross sectional area determines flow if the other factors remain constant, resistance in dynes varies directly rather than inversely with flow. The digital vascular resistance in dynes (see table 1) now becomes an intelligible proportion of the total systemic resistance in dynes, which can be calculated from the total systemic force at the sinuses of Valsalva to be approximately 1,732,640 dynes.* Such resistance is proportionately much higher per gram of fingertip than per gram of average tissue because of the greatly increased flow in the fingertip made possible by the arteriovenous anastomoses.

To complete the circle, resistance and force in dynes can each be divided by the actual cross sectional area to give

$$\frac{dynes}{cm.^2} = \frac{dynes}{cm.^2}$$

It will be recognized that in this sense pressure per unit of cross sectional area is exactly equal to resistance per unit of cross sectional area.

It can be seen from table 1 that vascular configuration volume index and caliber are decreased and resistance is increased in established hypertension. Also, a critical point in vascular configuration volume index, caliber and resistance in dyne second/cm.^{5} can be found, beyond which the cases of malignant hypertension fall. Resistance in dynes is more variable in malignant hypertension because of the variable decrease in flow and caliber. Resistance in dynes/cm.^{2} of cross sectional area is also more variable in malignant hypertension. In polycythemia on the other hand, if the viscosity factor is corrected in accordance with erythrocyte concentration[15] the vascular configuration volume index and caliber are approximately normal or slightly above normal despite moderately increased resistance. After phlebotomy all these values become normal.

Summary and Conclusions

1. The pressure-flow relationship in the dilated digital circulation at different levels of digital arterial pressure was found to be rectilinear in contrast to the logarithmic curvilinear relationship found by investigators perfusing the dog's leg. This difference is believed to be attributable to the fact that in the digit, after sympathetic nerve tone is released, the preponderance of flow is through arteriovenous anastomoses rather than capillaries.

2. By the application of Poiseuille's law to these data it is possible to calculate (a) digital vascular volume index in cubic microns, (b) initial digital vascular caliber in cm. of radius, (c) digital vascular resistance in dyne second/cm.^{5}, (d) in dynes and (e) in dynes/cm.^{2}.

3. The normal digital vascular volume index was found to vary from 1010 to 653 cubic microns, the digital vascular caliber from 0.031 to 0.028 cm. of radius, the digital vascular resistance in dyne second/cm.^{5} from 2,287,000 to 3,420,800, the digital vascular resistance in dynes from 235 to 301, and in dynes/cm.^{2} from 69,306 to 111,955.

4. In polycythemia the digital vascular volume index and caliber were normal or slightly above normal and remained normal after phlebotomy. The digital vascular resistance was either above or within normal limits but decreased to normal after phlebotomy.

5. In established essential hypertension the digital vascular volume index varied from 653 to 308 cubic microns. The digital vascular caliber varied from 0.028 to 0.023 cm. of radius, the digital vascular resistance in dyne second/cm.^{5} from 3,420,800 to 7,219,300, the digital vascular resistance in dynes from 301 to 406 and in dynes/cm.^{2} from 111,955 to 211,915. In the malignant phase of hypertension the digital vascular volume index was always below 308 cubic microns, the digital vascular caliber always below 0.023 cm. of radius and the digital vascular resistance in dyne second/cm.^{5} always above 7,219,300. The resistance in dynes varied from 286 to 357 and in dynes/cm.^{2} from 203,918 to 226,576.

Acknowledgments

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*See footnote on page 699.

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Kidney Function in Cor Pulmonale

Particular Consideration of Changes in Renal Hemodynamics and Sodium Excretion during Variation in Level of Oxygenation

By Alfred P. Fishman, M.D., Morton H. Maxwell, M.D., Charles H. Crowder, M.D., and Pablo Morales, M.D.

Renal hemodynamics and sodium excretion were investigated in two groups of patients with cor pulmonale: group 1 was in heart failure at the time of study, and group 2 had previously been in heart failure. These subjects, who were virtually or potentially in heart failure, were exposed to various levels of oxygenation in order to aggravate acutely or relieve their chronic anoxia. The compensatory adjustments in kidney function to these changes in oxygen tension and their implications constitute the substance of this report.

THE SEQUENCE of cardiodynamic events which terminates in cor pulmonale is initiated and perpetuated by pulmonary insufficiency and pulmonary vascular disease. The resultant anoxia, pulmonary hypertension, polycythemia, and hypervolemia not only contribute directly to the cardiac burden, but serve as stimuli to maintain each other. Anoxia is a highly significant factor in the genesis of cor pulmonale. Its role, for example, in causing polycythemia,[1] increase in coronary flow[2] and cardiac output[3] seems well established. In the subject who is chronically anoxic while breathing room air, the cardiopulmonary stresses of even slight activity cause further arterial desaturation. The effects of acute anoxia are thus superimposed upon the unremitting cardiac load of chronic anoxia. When chronic cor pulmonale has been established, the usual terminus is respiratory or circulatory failure.

The role of the kidney in cor pulmonale has not been adequately elucidated although isolated evaluations of renal function in individual patients have been reported. The present investigation was undertaken with several goals in mind. A prime purpose was the study of renal hemodynamics and sodium excretion in subjects with cor pulmonale. For comparison, these functions were determined in subjects who were, and in others who were not, in heart failure at the time of study. We hoped, by means of the results derived from these subjects who were virtually or potentially in heart failure, to clarify the renal contribution to the development of the congestive state in cor pulmonale.

In addition to measurements made at rest while breathing room air, renal function was similarly determined in these patients during exposure to gas mixtures containing oxygen concentrations which were either higher or lower than room air. The effects of anoxia on kidney function in normal subjects have been reported by Caldwell, Rolf, and White[4] and Berger, Galdston and Horwitz.[5] However, anoxia does not occur in the daily existence of the normal subject unless he ascends to high altitudes. Nor is it of significant degree in the subject in congestive heart failure due to the common causes (arteriosclerosis, rheumatic fever, etc.). Patients with cor pulmonale are not only chronically anoxic but are continually suffering periods of acute anoxia. We attempted by the use of low oxygen mixtures to reveal the renal mechanisms which are induced in

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Aided by a grant from the Commonwealth Fund.

these patients by the recurring daily episodes of acute arterial oxygen desaturation. Conversely, high oxygen mixtures were given in the attempt to unmask compensatory renal mechanisms which are continuously elicited by the chronic anoxia. Such mechanisms are not revealed by studies performed under the usual conditions of rest and room air.[6]

A parallel study of pulmonary function and cardiodynamics by cardiac catheterization was performed in the laboratory of Dr. A. Cournand. These results not only supplemented the clinical evaluation of our patients but also made possible a correlation between cardiac and renal function in cor pulmonale.

Clinical Subjects

Fifteen patients were included in this study. One patient, W. B., was studied twice, once while in the hospital and subsequently following restoration to ambulatory status. Approximately half of the subjects were derived from the wards or cardiac clinic of the First Medical Division (Dr. D. W. Richards, Jr.) of Bellevue Hospital. The others were made available to us by the Fourth Medical Division (Dr. F. A. Wilkinson) and the Dermatology Service. Six of the patients had been investigated by cardiac catheterization and pulmonary function studies in the Cardio-Pulmonary Laboratory of Dr. A. Cournand. They were referred to us for renal function tests by his associates, Drs. M. I. Ferrer, R. M. Harvey, and C. A. Webster.

The significant biographical and clinical data about each patient are included in tables 1 and 2. The subjects ranged in age from 21 to 74 years, but nearly all were over 45 years old.

For the purpose of comparison, the subjects were divided into three groups:

Group 1. Three subjects who were free from known heart or kidney disease and constitute, together with other normals studied in this laboratory, the control group. Subject W. K., suspected clinically of having generalized arteriosclerosis, may have had similar changes in the vessels of the kidneys.

Group 2. Nine subjects with cor pulmonale who had all been in heart failure at some time prior to study (table 2) but were not in heart failure at the time of study. Subject A. P. was of interest because an exsanguinating hemorrhage had reduced him hematologically from a state of polycythemia to anemia.

Group 3. Four subjects with cor pulmonale who were in heart failure at the time of study. Three were in heart failure despite treatment with digitalis, mercurials (stopped at least 10 days prior to the renal studies), low salt diet, bed rest, phlebotomy, and bronchial vasodilators. One subject (E. L.) had entered the hospital one week previously in manifest heart failure and was recovering from this initial attack of heart failure.

All of the above subjects were hospital patients except W. B. (no. 5), A. Y., D. C., B. B., and A. D., who came to the hospital solely for renal function tests.

In the patients with cor pulmonale, the clinical and x-ray diagnosis of chronic lung disease was confirmed by the pulmonary function studies done in Dr. Cournand's laboratory.[7] The subjects with pulmonary insufficiency due to emphysema showed the characteristic reduction in vital capacity, maximum breathing capacity, and arterial oxygen saturation, as well as an increase in arterial carbon dioxide content, a residual air greater than predicted, and a high alveolar nitrogen after seven minutes of breathing pure oxygen.[8] The one subject with diffusion fibrosis of unknown etiology (M. H.) characteristically failed to show any significant degree of pulmonary emphysema or spirometric evidence of ventilatory obstruction. Following exercise, the low level of resting arterial oxygen saturation (85 per cent) fell further to 62 per cent. Physiologically she represents an instance of diffusion fibrosis, with alveolar respiratory insufficiency.[9]

The criteria for the diagnosis of chronic cor pulmonale were those of the American Heart Association. These include chronic pulmonary disease, right heart enlargement (including right ventricular hypertrophy by electrocardiography), marked cyanosis, accentuated pulmonic second sound, and the absence of any other demonstrable etiology for the heart disease. In 3 of the subjects with cor pulmonale (M. H., M. M., and J. Mc.) the additional diagnosis of arteriosclerotic heart disease was suspected because of the patient's age. However, the clinical evolution in each instance was that of right heart failure, suggesting that arteriosclerotic heart disease contributed little, if at all, to the symptomatology. This was further substantiated by autopsy in patient J. Mc. one month after the renal function tests, where anatomic evidence for cor pulmonale with insignificant arteriosclerotic changes was found.

The functional and therapeutic cardiac classification represents the state of the subject at the time of study (table 1).

Three of the patients with cor pulmonale (W. B., M. H., J. Mc.) were studied by cardiac catheterization in Dr. Cournand's laboratory within 24

hours of the renal clearance studies. Three others (A. D., B. B., A. P.) had been similarly studied previously and because of the constancy of the measurements for cardiac output and intracardiac pressures it was felt that little more would be gained by another cardiac catheterization. Data on 2 of these patients, A. D. and B. B., are detailed elsewhere.[10] In no instance were renal clearance studies and cardiac catheterization attempted on the same day, since the combination of these procedures would increase the discomfort of the patients and promote an unsteady state. The data obtained by cardiac catheterization were used to supplement clinical criteria for cardiac failure and to obtain an integrated picture of the circulation in cor pulmonale. Since the subjects were exposed under similar circumstances to identical concentrations of inspired oxygen in both laboratories, comparisons were made of hemodynamic responses of the heart and kidneys to the various levels of oxygenation.

Regardless of the presence or absence of heart failure, and despite frequent phlebotomy, all of the subjects with cor pulmonale but 1 (A. P.) had increased hematocrits and total blood volumes at the time of study. Plasma volumes were less significantly increased. The low hematocrit in patient A. P. is ascribable to recent profuse epistaxes. All of the subjects with cor pulmonale also had some degree of arterial desaturation, ranging from 93 to 64 per cent, as contrasted with the normal arterial saturations in the control subjects. Despite the variation in salt intake, the serum sodium did not usually vary significantly from the normal. The individual values for serum sodium and protein are listed in table 1.

All of the patients were studied in the postabsorptive state. Although all the patients with cor pulmonale were receiving digitalis daily prior to study, none had received oral or parenteral mercurial diuretics for at least 10 days prior to study.

Methods and Materials

All studies were done in the morning on resting subjects at least 12 hours after the last meal. Hydration for the renal clearance studies was accomplished by the ingestion of two to four glasses of water the evening prior to the study, and the morning of the study. One to two glasses of water were administered at approximately hourly intervals during the study to maintain diuresis. Renal clearances were determined in the supine position, using inulin as a measure of glomerular filtration rate[11] and p-aminohippurate (PAH), at low plasma levels, to measure effective renal plasma flow (hereafter referred to as renal plasma flow).[12] By correction for hematocrit, determined in Wintrobe tubes after 30 minutes centrifugation at 3000 revolutions per minute, renal blood flow was calculated. The tubular excretory capacity (Tm) for PAH was calculated in 4 subjects where the load to Tm ratios exceeded 2.[11] Blood samples were collected into heparinized tubes from an indwelling brachial artery needle inserted under local Metycaine anesthesia at the start of the experiment. In each instance, following the establishment of adequate plasma levels by calculated priming injections, the concentrations were maintained by means of a constant infusion of these substances in water, delivered intravenously by a calibrated pump at the rate of 1.4 cc. to 2.8 cc. per minute. Retention catheters and bladder washouts with 30 to 60 cc. of distilled water followed by 30 to 60 cc. of air were used to collect the urine. For the determination of proteinuria, the diluted urines were evaporated to their original volumes in cellophane bags. Plasma concentrations were plotted semilogarithmically against time and the representative concentration extrapolated from the midpoint of each collection period.[13] All reported observations represent the average of two to four (usually three) clearance periods.

Following control studies on room air, renal clearances were repeated using various concentrations of inspired oxygen in nitrogen. These included 21 per cent, 30 per cent, 16 per cent, and 10 per cent, varying with the desired level of arterial oxygen saturation. In 1 patient with cor pulmonale (W. B.) and 1 control (W. K.) 38 per cent oxygen in helium was administered. The concentration of inspired oxygen and the resultant arterial oxygen saturation and pressure are indicated in table 2. The gas mixtures were administered by mouthpiece through demand-type valves, following application of a nose-piece. The method of administration of these mixtures for renal clearances was identical in every respect to that used for the determination of cardiac output and intracardiac pressures in these subjects and in a previous study.[6] Approximately two and one-half to five minutes of equilibration to a new gas concentration were permitted before the clearance period was started. The urine formed during the equilibration period was discarded. The total time of exposure to each level of oxygenation is indicated in table 2. The patient breathed room air without the mask for approximately 15 minutes between exposures to each successive oxygen mixture.

Renal vein catheterization was performed under fluoroscopy by the technic of Warren, Brannon and Merrill[14] to determine the renal extraction ratios of PAH at various levels of oxygenation. The position of the catheter in the renal vein was verified subsequently by the extraction ratios for oxygen. Mean blood pressures were obtained during each clearance period, using a calibrated aneroid manometer or mercury manometer connected to the brachial artery needle by a short rubber tube containing heparinized saline. Renal venous pressures and peripheral venous pressures were obtained using a saline manometer with the reference level 6.6 cm. below the angle of Louis.[15]

TABLE 1.—*Clinical and Chemical Data on Control Subjects and Patients with Chronic Cor Pulmonale*

Case Number	Patient	Age	Sex	Surface Area M.² BSA.	Diagnosis	Treatment Prior to Study	Hematocrit	Arterial Oxygen Capacity	Arterial Oxygen Saturation Room air	Plasma Volume cc./M.² BSA	Total Blood Volume cc./M.² BSA	Serum Sodium mEq./L.	Plasma Proteins
					Subjects without manifest cardiac or renal disease								
		Yrs.						*vol. %*	%				*gm. %*
1	D. D.	21	M	1.64	Eczema of hands bilateral	none	45.7	20.1	97	1735	2910	141	5.2
2	W. M.	52	M	1.71	Varicose ulcers lower extremities bilateral	none	46.0	16.1	96			143	5.9
3	W. K.	61	M	1.73	Varicose ulcers lower extremities bilateral Nutritional anemia Arteriosclerosis	none	31.6	12.6	97				6.5
					Previously in heart failure but not in failure at time of study								
4	W. B.	46	M	1.61	Bronchial asthma Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_B*	Digitalis Low sodium diet Phlebotomy Bed rest	51.0	21.5	93	1730	3907	136	6.8
5	W. B.	46	M	1.60	Bronchial asthma Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_B*	Digitalis Moderate salt intake Phlebotomy	47.4	21.5	93	1853	3360	141	6.8
6	A. P.	50	M	1.52	Chronic bronchitis Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_B*; 1 week following massive epistaxis	Digitalis Low sodium diet	33.2	13.3	90	1960	2978	142	7.9
7	A. Y.	38	M	1.47	Bronchial asthma Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_B	Digitalis Moderate salt intake Phlebotomy	59.8	20.4	82	1674	4440	145	7.5
8	J. Mc.	74	M	1.57	Chronic bronchitis Pulmonary emphysema Cor pulmonale† EH., NSR., compensated III_C	Digitalis Salt free diet	53.6	20.4	77	1773	3767	137	7.5

					III_C								
9	D. C.	50	M	1.85	Chronic bronchitis Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_C	Digitalis Salt poor diet Phlebotomy	51.3	21.2	87	2050	4400	139	5.9
10	A. A.	55	M	1.83	Pulmonary emphysema Cor pulmonale EH., NSR., decompensated IV_D Malnutrition	Digitalis Salt poor diet	51.1	19.5	82	2210	4710	141	7.6
11	B. B.	54	M	15.4	Bronchial asthma Pulmonary emphysema Cor pulmonale EH., NSR., compensated II_B	Digitalis Salt poor diet Phlebotomy	45.9	17.1	88	1950	3580	143	7.5
12	M. M.	65	M	1.27	Silicosis Pulmonary emphysema 6 weeks postmyocardial infarction ASHD., EH., NSR., decompensated IV_D	Digitalis Salt poor diet Phlebotomy	49.0	17.1	92	1648	3688	141	7.7
					In heart failure at time of study								
13	M. H.	64	F	13.9	Pulmonary fibrosis diffusion type Cor pulmonale EH., NSR., decompensated IV_D	Digitalis Salt free diet	52.0	19.8	85	1490	3090	148	6.3
14	S. P.	55	M	1.75	Chronic bronchitis Pulmonary emphysema Cor pulmonale EH., NSR., compensated III_C	Digitalis Salt free diet	60.3	25.3	86	1745	4720	135	4.1
15	A. D.	56	F	1.65	Bronchial asthma Pulmonary emphysema Cor pulmonale EH., NSR., decompensated IV_C	Digitalis Salt poor diet Phlebotomy	50.2	20.7	64	2080	4358	139	8.6
16	E. L.	52	M	2.17	Chronic bronchitis Pulmonary emphysema Cor pulmonale and ASHD., EH., AF., CI. decompensated III_C	Digitalis Salt free diet Bed rest	50.9	21.0	93	2420	5115	145	7.5

* American Heart Association Classification.

† Confirmed at autopsy 4 weeks after study.

These determinations were made while the patients were at rest, breathing room air.

TABLE 2.—*The Response of Renal Hemodynamics and Sodium Excretion to Variation in the Level of Oxygenation*

Case Number	Clinical Summary*	Concentration of inspired oxygen	Total time exposure	Arterial oxygen saturation	Arterial pO_2	Arterial CO_2 content	Renal plasma flow	Renal blood flow	Glomerular filtration rate‖	Filtration fraction	Mean blood pressure	Sodium excretion	Urine volume
	Subjects without manifest cardiac or renal disease												
		vol. %	*min.*	*%*	*mm. Hg*	*vol. %*	*cc./min.*	*cc./min.*	*cc./min.*		*mm. Hg*	*μEq./L.*	*cc./min.*
1	Dermatitis	21		97	100	45.4	710	1308	128	0.180	92	314.5	13.4
		30		98	105	44.6	718	1322	125	0.174	92	298.4	—
		21		97	100	—	711	1309	125	0.176	92	313.7	4.46
2	Varicose ulcers	21		97	—	46.2	519	961	120	0.231	96	83.1	12.62
		30		97	—	45.7	520	962	118	0.227	94	75.8	13.26
		10		—	—	44.6	495	917	107	0.216	96	115.6	10.09
		21		—	—	—	501	928	106	0.211	96	87.0	—
3	(1) arteriosclerosis	21	33	97	98§	44.1	408	596	111	0.272	89		12.6
	(2) dermatitis	38	29	—	—	43.7	425	621	111	0.259	89		12.6
	(3) anemia	10	28	91	64§	—	469	686	124	0.265	88		8.7
		30	39	—	—	—	435	636	107	0.247	84		7.18
		38	35	—	—	—	433	633	107	0.246	86		4.5
	Previously in heart failure but not in heart failure at time of study												
4	Cor pulmonale; previously in heart failure, 1 year†	21	30	93	74§	52.6	438	894	130	0.297	92	80.0	2.6
		38	49	96	105§	52.8	417	850	135	0.324	90	33.0	2.5
		30	39	96	105§	52.0	407	831	125	0.307	91	71.9	2.2
		16	33	81	40§	50.3	453	924	130	0.287	93	90.8	1.8
		38	39	97		52.8	340	694	132	0.388	92	54.8	2.2
5	Cor pulmonale; previously in heart failure, 1 year	21	37	93	74§	53.9	495	941	131	0.265	92	146.5	3.5
		30	32	96	110§	58.1	468	890	132	0.282	88	127.8	7.3
		16	27	81	41§	56.3	493	937	125	0.254	91	212.6	5.7
6	Cor pulmonale; after hemorrhage, previously in heart failure, 9 months	21	44	90	63§	58.6	417	624	92	0.221	82	68.5	3.1
		30	42	97	98§	59.2	314	470	75¶	0.239	84	47.6	2.1
		16	34	81	45§	57.4	374	560	100	0.267	84	67.8	2.5
7	Cor pulmonale; previously in heart failure, 15 months	21	45	87	55§	57.1	447	1085	104	0.232	88	142.5	3.9
		16	34	70	37§	54.0	633	1536	127	0.201	81	199.8	3.6
		30	45	97	99	54.6	446	1083	106	0.238	87	103.5	3.4
8	Cor pulmonale; previously in heart failure, 1 year	21	99	77	42	65.8	649	1400	108	0.166	81	110.0	1.39
		30	40.5	95	83	63.6	666	1435	110	0.165	81	109.8	0.87
9	Cor pulmonale; previously in heart failure, 6 months	21	62	87	55§	40.0	401	823	99	0.247	98	171.4	1.27
		16	20	76	41§	39.6	400	821	90	0.225	98	203.8	1.20
		30	36	98	105	40.2	335	688	91	0.272	96	98.6	0.70
		21	41	87	55	40.0	383	786	95	0.248	94	149.5	0.48

10	Cor pulmonale; recovered from first attack heart failure, 2 weeks	21	38	82	47	66.4	313	640	130	0.415	102	144.2	1.68
		30	42	90	63	66.6	279	571	110	0.394	106	89.8	2.58
		16	15	75	40	65.7	322	658	109	0.339	100	123.0	1.95
11	Cor pulmonale; previously in heart failure, 1 year	21	61	88	57	60.5	341	630	123	0.365	102	145.8	1.85
		30	30	95	91	64.8	236	436	105	0.447	100	96.1	2.64
		21	16	89	60	60.5	338	625	107	0.316	102	100.5	2.05
		16	26	38	21	54.7	393	726	104	0.265	100	152.2	2.27
		21	27	88	57	60.5	340	628	104	0.306	100	147.2	
12	Cor pulmonale, ASHD, previous myocardial infarction; persistent heart failure despite treatment	21	46	92	68	62	321	630	77	0.239	94	93	3.78
		30	42	95	85	59.3	286	561	80	0.280	94	85.3	5.95
		16	15	80	45	56.2	333	654	81	0.243	98	152.7	3.32
		21	25	92	68	62	280	558	81	0.289	93	104.9	1.34
	In heart failure at time of study												
13	Cor pulmonale; persistent heart failure despite treatment	21	72	85	49§	49.6	210	438	57	0.271	88	65.6	1.17
		30	52	97	84§	50.7	185	385	61	0.330	86	52.1	0.28
		16	30	68	36§	51.2	207	432	59	0.285	92	58.2	1.41
14	Cor pulmonale; persistent heart failure despite treatment	21	41	86	53§	57.1	196	494	58	0.296	104	53.9	1.10
		16‡	40	76	41§	54.8	170	428	59	0.347	76	26.0	0.71
		30	50	91	65§	57.2	182	458	58	0.319	98	8.9	0.53
		21	45	86	53§	57.1	229	577	58	0.253	94	14.9	0.63
15	Cor pulmonale; persistent heart failure despite treatment	21	37	64	33	67.8	280	562	69	0.246	84	124.9	3.33
		30	45	90	63	68.2	245	492	71	0.290	90	94.8	3.38
		16	19	57	29	66.4	280	562	68	0.243	88	138.4	3.87
		21	40	93	73§	49.4	183	373	82	0.448	103	28.3	1.4
16	Cor pulmonale and ASHD; during recovery from first attack of heart failure	16	25	84	51§	44.9	211	430	84	0.398	103	73.2	1.6
		30	32	97	100	49	155	316	84	0.541	106	29.7	1.1
		16	25	86	53§	42.9	189	385	80	0.423	104	61.1	1.28
		14	32	82	47§	48.4	194	395	79	0.407	106	83.8	0.72

The subjects are listed consecutively as in table 1.

* Detailed in table 1; 'normal' indicates absence of cardiac or pulmonary disease.

† Since last episode of heart failure.

‡ During vasovagal reaction.

§ Determined by methods of Riley; others by pH and oxyhemoglobin dissociation curve.

‖ Clearances as averages of two to four consecutive periods.

¶ This depression of GFR with 30 per cent oxygen was not observed at Tm levels of PAH.

The cardiac catheterization studies were identical with those previously described from Dr. Cournand's laboratory.[10]

Inulin was determined by a modification of Harrison's method as described by Goldring and Chasis.[12] PAH, free and conjugated, was determined by the method of Smith and associates.[16] Blood samples for oxygen determination were drawn anaerobically and were analyzed in duplicate by the method of Van Slyke and Neill.[17] The arterial partial pressure of oxygen was determined directly by the method of Riley[18] or calculated from the arterial oxygen saturation and pH as determined by the glass electrode. Total proteins were determined from plasma specific gravities by the method of Van Slyke and co-workers.[19] Blood volumes were determined, using T-1824, by the method of Noble and Gregersen.[20] The mean normal values for total blood and plasma volume are 2900 cc. and 1600 cc., respectively, per square meter of body surface. Sodium in blood and urine was determined with a Perkin-Elmer internal standard flame photometer model 52-A.

Results

The changes in renal circulation, mean blood pressure, and sodium excretion as related to each level of oxygenation are presented in table 2. The pattern of change is illustrated in figures 1 and 2.

In contrast to the 3 control subjects, all patients with cor pulmonale had some degree of arterial desaturation at rest (64 to 93 per cent). Following exposure to 16 per cent oxygen in nitrogen, significant depression of arterial saturation occurred in all subjects with pulmonary disease; the lowest levels were reached in 2 patients with heart failure (M. H. and E. L.) where saturations of 68 and 57 per cent respectively were reached. These oxygen saturations corresponded to a partial pressure of oxygen of 36 and 29 mm. Hg respectively. Following the administration of 30 per cent oxygen in nitrogen, most of the subjects were restored to normal arterial oxygen saturation. Some, particularly the subjects in heart failure, failed to reach normal arterial oxygen saturations and pressures while breathing the 30 per cent oxygen mixture.

In most of the subjects with cor pulmonale, the arterial carbon dioxide content was greater than normal. The hyperventilation associated

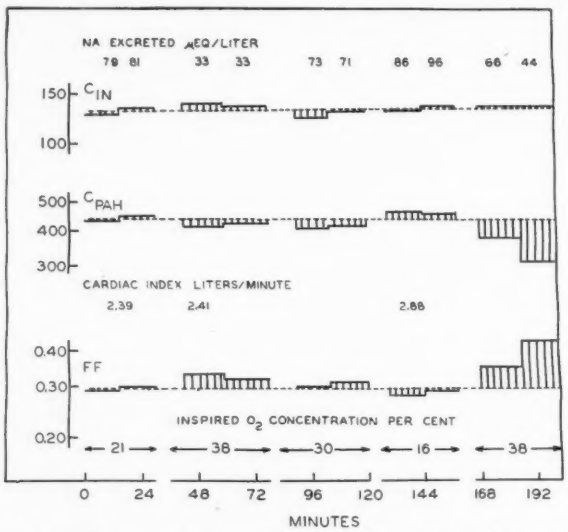

FIG. 1. Renal hemodynamics and sodium excretion in W. B., a subject with cor pulmonale who had previously been in heart failure but was not in heart failure at the time of study. The responses to variation in level of oxygenation are illustrated. Significant depression of renal plasma flow and increase in filtration fraction occur during increase in arterial oxygen tension; oppositely directed changes occur in response to acute anoxia. Sodium excretion varies in the same direction as renal plasma flow. Discussed in text.

with the administration of 16 per cent oxygen usually caused a fall in arterial carbon dioxide content; during 30 per cent oxygen the arterial carbon dioxide content tended to be unchanged or increased.

In 2 of the 3 control subjects there was no significant variation in renal plasma flow or glomerular filtration rate at any new level of oxygenation. In W. K. the administration of 10 per cent oxygen resulted in slight parallel increases in renal plasma flow and glomerular filtration rate above control values. Much more striking was the increase in sodium excretion (39 per cent) (table 2). The renal plasma flow determined under the usual conditions of rest and room air was markedly decreased in the subjects with heart failure. It varied from low to normal values in the subjects with cor pulmonale who were not in failure.

In both of these groups, the pattern of response of the renal plasma flow to variation in level of oxygenation was similar, regardless of the presence or absence of heart failure. Following high oxygen, renal plasma flow decreased significantly from control values at room air in all subjects but one (J. Mc.); following low oxygen the renal plasma flow tended to increase but the changes were far less striking than after high oxygen. There was no instance of decrease in renal plasma flow in response to anoxia except in patient S. P., who went into shock. The most marked increases in renal plasma flow occurred when 16 per cent oxygen was administered directly following 21 per cent oxygen. When 16 per cent oxygen was administered following an intervening exposure to 30 per cent oxygen, even though renal plasma flow increased as compared with the previous high level of oxygenation, it occasionally failed to exceed control measurements obtained in room air (A. P.). In brief, renal plasma flow appeared to vary inversely with change in oxygen tension (fig. 3). However, no direct proportionality, and even an occasional lack of response to variation in oxygenation, was observed. Only 1 subject (S. P.) who re-

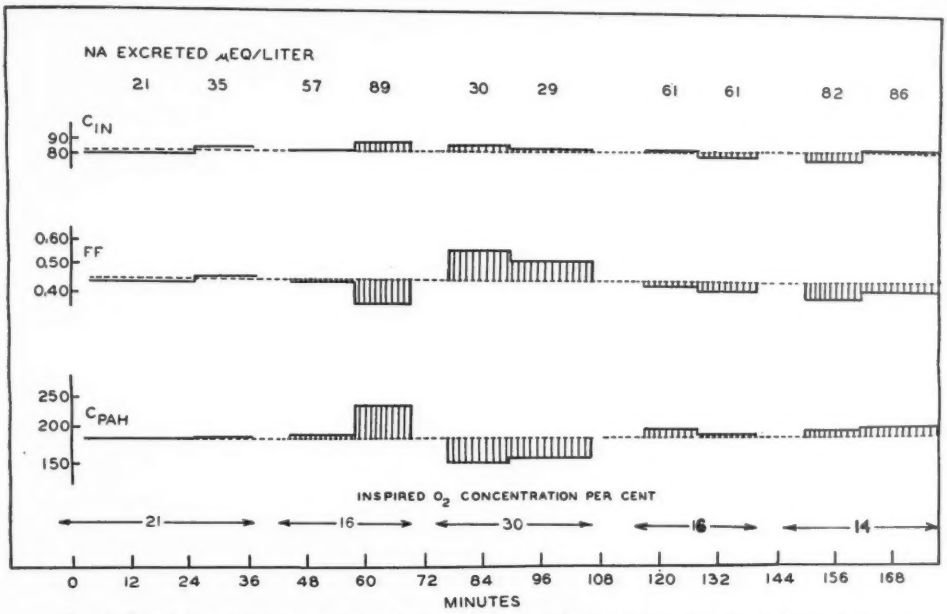

FIG. 2. Renal hemodynamics and sodium excretion in subject E. L., who was in heart failure at the time of study. The pattern of response is similar to that observed in patients with cor pulmonale who have recovered from an episode of heart failure (fig. 1). The influence of previous levels of oxygenation on renal plasma flow and sodium excretion are illustrated. Discussed in text.

sponded to anoxia with a fall in blood pressure, differed significantly from the general pattern of response of renal plasma flow to change in arterial oxygen tension. We made no attempt to establish a critical level of oxygenation for change in renal blood flow because of the small number of observations.

The glomerular filtration rate was depressed in the 4 subjects with heart failure, as measured under the usual conditions of rest and room air. It did not vary significantly in them, or in 5 of the 9 subjects who were not in heart failure following change in level of oxygenation. In the other 4 subjects with cor pulmonale (none of whom were in heart failure) signifi-

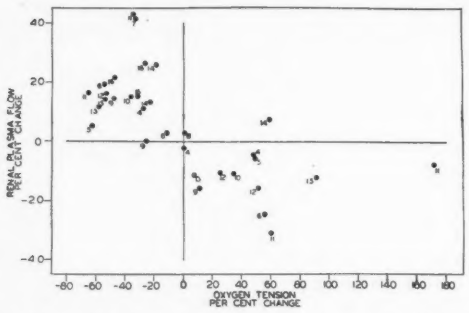

FIG. 3. The response of the effective renal plasma flow to change in arterial oxygen tension. In general, renal plasma flow varies inversely with change in arterial oxygen partial pressure, but there is no absolute proportionality. Patient S. P. (14) went into shock during exposure to low oxygen tension.

cant change took place (−18 to +22 per cent) and the direction of change paralleled but did not exceed the corresponding change in renal plasma flow. The filtration fractions, the ratio of glomerular filtration rate to renal plasma flow, at successive levels of oxygenation are indicated in table 2.

Sodium excretion was measured in 2 of the 3 control subjects. There was no significant change following exposure to high oxygen. In the third control subject, W. M., following 10 per cent oxygen, a significant increase occurred without any corresponding increase in filtration rate or renal plasma flow.

In the subjects with cor pulmonale, sodium excretion increased following 16 per cent oxygen in all subjects except S. P., who developed a concomitant fall in blood pressure and renal blood flow. As in the case of the renal plasma flow, the increase in sodium excretion during anoxia was much less marked if a period of high oxygen preceded the exposure to room air and subsequent anoxia. It is of interest that in patient W. B. the administration of 30 per cent oxygen after 38 per cent resulted in increased sodium excretion. Exposure to high oxygen tended to depress sodium excretion.

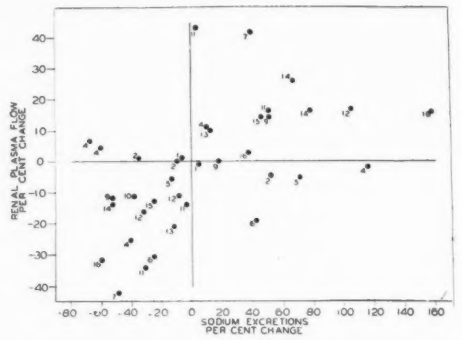

FIG. 4. The effective renal plasma flow and sodium excretion at various levels of oxygenation. In general, the two phenomena vary directly but not proportionally. Discussed in text.

TABLE 3.—*The Maximal Range of Tubular Excretion at Various Levels of Oxygenation*

The physiologic and biographic data of these subjects are presented in detail in tables 1 and 2. The load:Tm ratio is calculated according to Smith.[11] There is no significant change in Tm following exposure to high or low oxygen concentrations.

	Diagnosis	Concentration of inspired oxygen	PAH load: Tm	PAH Tm
		per cent		
D. D.	Control	21	3.60	70.8
		10	3.68	71.5
A. P.	Cor pulmonale	21	4.60	65.6
		30	2.60	62.0
		16	2.80	59.2
A. Y.	Cor pulmonale	21	4.40	102.7
		16	6.80	101.2
		30	4.60	98.1
M. H.	Cor pulmonale in heart failure	21	3.20	67.6
		30	2.70	60.9
		16	3.20	61.5

The changes in sodium excretion were more marked (as were the changes in renal plasma flow) when compared with the immediately preceding level of oxygenation rather than with the original or final control values. The changes in glomerular filtration rate were not consistently related to corresponding changes in sodium excretion. In general, the direction of change in sodium excretion paralleled changes in renal blood flow (fig. 4), but there was no proportionality in degree of change.

The tubular excretory mass (Tm) was studied in 6 subjects at various levels of oxygenation. The load:Tm ratio was adequate in the 4 subjects (including 1 control and 1 subject with heart failure) presented in table 3. It is apparent that there was no significant change in Tm at the various levels of oxygenagion.

TABLE 4.—*Extraction Ratios for PAH in 5 Subjects with Cor Pulmonale in Heart Failure*

Position in renal vein identified by fluoroscopy and confirmed by oxygen extraction ratios.

	Age	Concentration of inspired oxygen	Renal plasma flow	Extraction ratio PAH
	years	*per cent*	*cc./min.*	
J. H.	66	21	255	0.92
J. L.	54	21	124	0.76
J. D.	68	21	162	0.71
S. P.	55	21	196	0.86
		16*	170	0.86
		30	182	0.86
E. L.	57	21	183	0.91
		16	211	0.92
		30	155	0.91

* Developed shock-like state while breathing 16 per cent oxygen

The extraction ratios for PAH were determined in 5 subjects with cor pulmonale in heart failure, including 2 subjects studied at various levels of oxygenation. The data are indicated in table 4. The extraction ratios ranged from 71 to 92 per cent, with an average of 81 per cent. There was no change in extraction ratio with variation in level of oxygenation, even though patient S. P. developed a shock-like state while breathing 16 per cent oxygen.

TABLE 5.—*The Relation of Cardiac Output to Blood Flow through the Kidney at Various Levels of Oxygenation*

Following increase in arterial oxygen saturation, the renal fraction decreases, indicating a greater increase in resistance to flow through the kidney than in over-all peripheral resistance. Patients M. H. and A. D. were in heart failure at the time of study.

	Concentration of inspired oxygen	Arterial oxygen saturation	Mean blood pressure	Renal blood flow	Cardiac output	Renal fraction RBF: CO
	per cent	*per cent*	*mm. Hg*	*cc./min.*	*cc./min.*	
M. H.	21	79	88	438	3570	12.3
	30	95	86	385	3420	11.3
W. B.	21	90	92	894	3850	23.2
	30	96	90	831	3880	21.4
	16	80	91	924	4630	20.0
A. P.	21	90	82	624	4110	15.2
	30	97	84	470	4120	11.4
	16	81	84	560	4050	13.8
J. Mc.	21	80	81	1400	4700	29.8
	30	88	81	1435	4540	31.6
B. B.	21	90	103	630	5120	12.3
	16	87	103	726	5690	12.8
	21	90	104	628	5310	11.8
	30	92	106	436	4920	8.9
A. D.	21	75	84	562	5590	10.1
	30	92	90	492	5380	9.1
A. Y.	21	85	88	1085	7100	15.3
	30	93	87	1083	7180	15.1

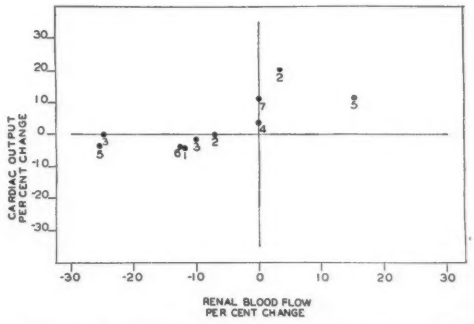

FIG. 5. Comparison between change in cardiac output and change in effective renal plasma flow at the various levels of oxygenation. The clinical and chemical states of these subjects are included in tables 1 and 2. The lack of constant parallelism in the direction and degree of change suggests that the change in cardiac output is not the sole determinant of the change in renal plasma flow. Discussed in text.

In table 5 is presented a comparison of renal blood flow and cardiac output measurements,

conducted under similar protocols but not simultaneously, in 7 subjects with cor pulmonale. The renal fraction (per cent of the cardiac output flowing through the kidney) showed a decrease (most marked in A. P. and B. B.) in all subjects but one (J. Mc.) during values in the same direction but varied in degree; 2 other patients, similarly exposed, increased their cardiac outputs without corresponding alteration in renal plasma flow; 5 subjects exposed to high oxygen manifested a considerable fall in renal plasma flow without

TABLE 6.—*A Comparison of Mean Segmental Renal Vascular Resistances in Normal Subjects, Patients with Cor Pulmonale Recovered from Heart Failure, and Cor Pulmonale in Heart Failure*

Two illustrative cases from each group are detailed in the middle third of the chart. The lower third contains the responses of two subjects with cor pulmonale, one with and the other without heart failure, to variation in the arterial oxygen saturation.

Diagnosis	Subject	Arterial oxygen saturation	Mean blood pressure	Filtration rate	Renal blood flow	Afferent resistance	Efferent resistance	Venular resistance	Total renal resistance
Mean values									
		per cent	*mm. Hg*	*cc./min.*	*cc./min.*	*dynes per sec. per cm.$^{-5}$*			
Normal* (average of 22 subjects)		96	91	128	1098	2005	2271	2244	6281
Cor pulmonale (average of 9 subjects)		87	92	121	938	2191	2709	3094	7915
Cor pulmonale in heart failure (average of 4 subjects)		82	95	65	473	6414	2935	6069	15670
Illustrative cases									
Normal	D. D.	96	92	128	1308	1939	2377	1062	4635
Normal	W. M.	96	96	122	961	2961	1965	1965	7012
Cor pulmonale†	W. B.	92	92	130	894	1780	2829	2563	6759
Cor pulmonale†	A. V.	88	88	104	1085	1115	1753	2058	5007
Cor pulmonale in heart failure	M. H.	88	88	57	438	4515	2497	3957	1740
Cor pulmonale in heart failure	S. P.	104	104	58	494	7835	2204	5524	1013
Effect of change in arterial oxygen saturation in cor pulmonale									
Cor pulmonale†	W. B.	93	92	130	894	1726	2829	2563	6760
		81	93	130	924	1859	2722	2470	6640
		96	91	135	725	1859	3904	3705	10372
Cor pulmonale in heart failure	E. L.	93	103	82	373	11421	4675	9017	21380
		84	103	84	430	10220	4037	8300	20850
		97	106	84	316	12222	6335	12461	29350

* Indicates freedom from detectable cardiac or renal disease

† Previously in heart failure but not in failure at time of study

during exposure to high oxygen. There was no consistent change in the renal fraction during exposure to acute anoxia.

The lack of absolute correlation between cardiac output and renal plasma flow following change in level of oxygenation is indicated in figure 5. Thus, in 2 subjects during acute anoxia, both flows increased above control significant change in cardiac output. Renal plasma flow appeared to be much more influenced by the previous level of oxygenation than was the cardiac output. The greatest increase in renal plasma flow during acute anoxia was observed when 16 per cent oxygen was administered directly after 21 per cent without previous exposure to high oxygen concentra-

tions. In subject A. P., where exposure to 30 per cent oxygen preceded the 21 and 16 per cent concentrations, the renal plasma flow response to anoxia was depressed below control levels. This sequence also occurred, but to a lesser degree, in subject W. B. In these 2 subjects, there was considerable disparity between the degree of response of the cardiac output and renal plasma flow to the anoxia which followed a previous, but not immediately preceding, exposure to high oxygen concentrations.

In table 6 are presented the contributions of the segmental renal vascular beds to the resistance to blood flow through the kidneys, as calculated by the equations of Gomez.[21, 22] The data from which these resistances were calculated are included in tables 1 and 2. The total renal resistances and the relative resistances of the afferent, efferent, and venular segments, are similar in the normal subjects and the subjects with cor pulmonale who were not in heart failure. The subjects who were in heart failure during the study had increased total renal resistances to blood flow, chiefly ascribable to increases in afferent arteriolar and venular resistance. In both groups of patients with cor pulmonale the total renal resistance increased following elevation of the level of arterial oxygen saturation. The most marked changes occurred in efferent arteriolar and venular resistances. The changes of renal resistance in response to anoxia were less clearly defined than the changes in response to high oxygen, and were influenced by the previous levels of oxygenation. The total resistance following anoxia remained unchanged or decreased.

In 4 of 5 subjects with marked arterial desaturation, including 2 with heart failure (M. H. and A. D.), no protein could be demonstrated in the urines which were obtained while the subjects were breathing 21 or 30 per cent oxygen. In 1 subject (A. D.), following subsequent exposure to 16 per cent oxygen, proteinuria appeared as detected by boiling and acidification of the urine and confirmed by the biuret reaction. The proteinuria persisted despite the administration of 21 and 30 per cent oxygen. A protein-free urine specimen was obtained the next day while the patient was at rest and breathing room air.

The true urine volumes are presented in table 2. The variations observed could not be related to level of oxygenation.

Discussion

We have studied the renal function in two groups of patients with cor pulmonale; one group was in heart failure at the time of study, the other group had recovered from at least one previous episode of heart failure but was not in heart failure at the time of study. Our initial considerations are of measurements made while these chronically anoxic subjects were breathing room air. Subsequently we shall consider the effects of variation of arterial oxygen tension on renal function in these subjects.

Because of pulmonary insufficiency and pulmonary vascular disease, these patients with cor pulmonale are, in certain respects, physiologically different from patients with other types of heart disease. The distinguishing characteristics vary in degree from subject to subject, but include marked arterial oxygen desaturation, polycythemia, frequent increase in cardiac output, and a relatively low peripheral resistance.

These factors may, individually or in combination, influence blood flow through an organ. However, in subjects with cor pulmonale, the advent of heart failure apparently minimizes the influence of these characteristics on the kidney and the renal hemodynamics resemble the hemodynamics described in subjects with heart failure of other cause.[23, 29] The renal plasma flow is depressed below normal, the high hematocrits in subjects with cor pulmonale causing a proportionally greater reduction in renal plasma flow than blood flow. The glomerular filtration rate is also reduced, less consistently and to a lesser degree than the renal plasma flow; the filtration fraction (per cent of plasma water filtered at the glomerulus) is consequently increased.

The part played by each of the vascular segments of the kidney in effecting the characteristic reduction in renal plasma flow and increase in the filtration fraction have not been well defined. Constriction of the efferent ar-

teriole, with increase in intraglomerular pressure, have been generally implicated as the predominant vasomotor mechanisms of the kidney during heart failure[22]; to the increase in venous pressure at the vascular outlet of the kidney has been attributed a lesser role.[25]

This paramount role generally ascribed to the efferent arteriole in determining the resistance of the kidney to blood flow in the presence of heart failure is open to question. The hemodynamic principles which govern the flow of blood through the kidney have been presented by Gomez.[24] Formulas derived by him from these principles have been utilized for the calculation of segmental renal vascular resistances in subjects with congestive heart failure, including our subjects with cor pulmonale.[21] These results suggest that the afferent arteriole is the site of predominant intrarenal vasoconstriction, the efferent arteriolar and venular resistances apparently contributing in lesser degree to the increase in total renal resistance to blood flow.[21]

After clinical recovery from heart failure the subjects with cor pulmonale often have persistent diminution in renal function, chiefly, but not solely, manifested by decreased renal plasma flow. Glomerular filtration rate is less consistently depressed. A similar depression of renal function has often been noted in patients who have clinically recovered from heart failure of other cause, for example, rheumatic fever.[22] The cause for these impaired renal functions after restoration of cardiac compensation is not known. Since comparable studies of renal function were not performed in our subjects prior to the onset of heart failure, we cannot state whether the impaired functions are due to emotional factors initiated by the study,[11] clinically unrecognizable renal disease, arteriosclerotic or degenerative changes of the kidneys, or the previous heart failure. For example, one control subject, W. K., with no overt evidence of intrinsic renal disease, was found to have a depression of renal blood flow similar to that observed in our compensated cardiac patients. The diminution in renal function incident to advancing age has recently been stressed by Davies and Shock.[26] We attempted to compare renal function in our subjects with the younger anoxic and polycythemic subjects of Scott and Elliott.[27] The difference in age distribution between the two groups constitutes a significant barrier to any such comparison.

We have indicated above that, because of the high hematocrits, the depression of renal plasma flow below normal is more striking than depression in renal blood flow. The effect of polycythemia (in the presence of normal serum protein concentrations) on the resistance to flow of blood through the kidney is difficult to evaluate. Scott and Elliott[27] believed that polycythemia caused preferential increase in resistance to flow in the efferent arteriolar or postglomerular segments. This interpretation is difficult to reconcile with the normal or elevated renal blood flows in their subjects. Selkurt[28] found that alteration in viscosity induced by rapid whole blood transfusion in dogs had little effect on their renal blood flow. One of our subjects (A. P.), who had a series of severe and almost exsanguinating epistaxes during the week prior to study, manifested a persistent reduction in renal plasma and blood flow despite severe anemia and freedom from heart failure. These observations suggest that the reduction in renal blood flow is apparently determined by factors other than increased red cell mass per se.

Most of the subjects with chronic congestive heart failure of more common cause (arteriosclerotic, rheumatic, hypertensive, etc.) have reduced cardiac outputs; peripheral vasoconstriction serves to maintain their mean blood pressure at normal levels. The renal blood flow is reduced more than the cardiac output by preferential vasoconstriction of the renal vessels.[29] As indicated above, the same general pattern of kidney function exists in subjects with cor pulmonale who develop heart failure, despite the presence of a high cardiac output. In this group of patients the peripheral resistance is comparatively lower than in the group with low cardiac output failure but the selective deviation of blood away from the kidney is still manifest.

The diminution in blood flow through the

kidney is accomplished by constriction of the vascular segments of the kidney, chiefly the afferent and venular (postefferent arteriolar) segments. Although the afferent arteriolar vasoconstriction found in subjects with heart failure resembles that observed in essential hypertension,[21] no significant hypertension is usually associated with heart failure. Our results suggest that the afferent arteriolar segments of the kidney participate, as do the arterioles elsewhere in the body, in the systemic vasoconstriction which characterizes congestive heart failure. The efferent arterioles of the kidney respond similarly but to a lesser degree. The increased venular resistance (the resistance to flow between the efferent arteriole and the inferior vena cava) is believed to be caused not only by the elevation of the venous pressure per se, but also by an increase in the interstitial pressure of the kidney.[21]

The three groups of patients (2 with cor pulmonale and 1 control) included in this study were exposed to various consecutive levels of oxygenation. Our purposes in acutely inducing or relieving anoxia were indicated above. We recognize that our evaluation of the sequelae of acute anoxia (to be presented below) has not dissociated the contribution of the depression of arterial carbon dioxide partial pressure increase in blood pH, and compensatory hyperventilation from the effects of acute oxygen lack. Similarly, in the consideration of the results of increase in arterial oxygen saturation we have not identified in detail the role of the depression of respiration usually associated with the relief of anoxia. The influence of tissue metabolites and enzyme systems induced by the conditions of our experiments also evades analysis. The significance of these various collateral effects in mediating the circulatory phenomena which result from acute change in level of oxygenation are difficult to assess. For example, McCance and Widdowson[30] found that hyperventilation (a usual side effect of acute anoxia in our subjects) was capable in normal subjects of causing an increased excretion of sodium and potassium. Consequently the data recorded by us during acute variation in the level of oxygenation reflect not only the direct results of oxygen increase or lack, but also the concomitant results of variation in local tissue factors and blood carbon dioxide tensions.

With this reservation in mind, the general pattern of response to anoxia in the subjects with cor pulmonale, regardless of the state of cardiac sufficiency, seemed consistent. During acute anoxia, there was no decrease in renal plasma flow or sodium excretion except in the 1 subject who sustained partial circulatory collapse while breathing a 16 per cent oxygen mixture. The other subjects responded to anoxia by an increase in renal plasma flow and sodium excretion above the values recorded at the previous level of oxygenation. The glomerular filtration rate showed a more variable response, frequently an increase. These patterns are similar to those observed in normal subjects by Berger and co-workers,[5] and in patients with congestive heart failure due to valvular disease by Aas and Blegen.[31] It is clinically recognized that the chronic anoxia associated with chronic pulmonary or congenital cardiac disease does not, per se, lead to edema. The increase in sodium excretion and renal blood flow observed in our chronically anoxic subjects during exposure to low oxygen tensions is diametrically opposed to the renal ischemia and sodium retention regularly associated with heart failure. These findings in anoxic subjects who are virtually or potentially in heart failure suggest that anoxia, per se, plays little role in the precipitation or furthering of the congestive state.

Epinephrine has been suggested as the mediator of the circulatory responses to anoxia.[32, 33] The effects of epinephrine on the hemodynamics of the kidney are available elsewhere,[21, 22] and include renal ischemia and increased resistance to flow. Renal ischemia and increased resistance did not occur following anoxia, suggesting that epinephrine plays no significant role in the renal response to anoxia.

The factors responsible for the increased sodium excretion during acute anoxia are not known. The significance of hyperventilation[30] has been presented above. Burrill, Freeman, and Ivy exposed normal subjects to simulated

altitude and described an increase in the excretion of sodium and potassium in the urine during acute anoxia.[34] They concluded that this electrolyte pattern excluded a significant role of the adrenal cortex in the response to acute anoxia. Despite the temporary increase in sodium excretion during the two hours of the exposure to altitude, the total 24 hour sodium excretion was not increased above control values.

Although there is a general trend in cor pulmonale for sodium excretion and renal blood flow to vary in the same direction, there is no direct proportionality in their responses to variation in level of oxygenation. It seems probable that both are responding to a stimulus associated with the acute aggravation or relief of anoxia. Despite the established influence of other hemodynamic phenomena, such as elevation of venous pressure on sodium excretion by the kidney, we cannot relate sodium excretion to renal plasma flow except possibly through the medium of the glomerular filtration rate. However, the glomerular filtration rate in this study had no consistent relation to sodium excretion. The venous pressure, as measured in the right auricle[6] did not significantly vary in these experiments, thus excluding another factor capable of influencing sodium excretion. The intimate mechanisms causing variation in sodium excretion in these subjects were not identified.

The partial or complete restoration of arterial oxygen tensions to normal by the administration of gas mixtures rich in oxygen had a more marked and consistent effect on renal blood flow than did the augmentation of anoxia by use of oxygen-poor mixtures. As normal arterial oxygen tensions were approached, renal blood flow fell and renal resistance to flow increased. The depressant effect of increased oxygenation on renal blood flow suggests that in these chronically anoxic subjects renal blood flow was increased in response to oxygen lack; the relatively high oxygen requirements of the kidneys are thus apparently met by polycythemia, small renal arteriovenous oxygen difference, and a sustained increase in renal blood flow. The acute relief of anoxia accomplished by exposure to high oxygen tensions apparently removes the stimulus for renal hyperemia. The depressant effect of increased oxygen tensions on renal blood flow persisted even after the patients were again allowed to become anoxic by exposure to room air. It was previously indicated that aggravation of anoxia by exposure to low oxygen tensions generally increased renal blood flow; the effect of acute anoxia was minimized by an antecedent exposure to high oxygen tensions. The mechanism for the persistent depression of renal blood flow by increased oxygenation in these subjects is not clear.

At least three factors suggest themselves as possible mechanisms for alteration in renal blood flow in response to change in level of oxygenation: (1) parallel changes in blood pressure, (2) parallel and passive changes in renal blood flow and cardiac output, and (3) alteration in the capacity of the renal tubule to extract PAH from the circulating blood, thus invalidating the use of uncorrected renal clearances as measurements of renal plasma flow.

There were no consistent changes in the systemic blood pressure (the perfusion pressure of the kidney) in response to variation in oxygenation.

In view of the previously demonstrated capacity of the kidney to influence its blood flow autonomously,[11] it appeared unlikely that renal blood flow would mirror changes in cardiac output. Our data (renal fractions and resistances) indicate that blood flow through the kidney is not a passive phenomenon which is solely determined by the output of the heart. Although cardiac output and renal blood flow tend to vary in the same direction in response to variation in level of oxygenation,[6] the degrees of change are not proportional and often one changes without the other. The cardiac output may contribute to but does not determine the response of the renal blood flow to acute change in oxygenation.

The validity of our measurement of the renal plasma flow by PAH clearance at successive levels of oxygenation, employing subjects with and without heart failure, depends on the integrity of the extraction ratio for PAH under these circumstances. Merrill and Cargill[35] and others[15] have determined the extraction ratios

of PAH in subjects with heart failure and were unable to demonstrate any significant difference from values obtained in normal subjects. We studied 5 subjects with cor pulmonale in heart failure who were at rest and breathing room air. In 2 the extraction ratios were somewhat lower than normal; in 3 the extraction ratios were normal. Variation of the level of oxygenation in 2 of the subjects failed to cause any significant change in the extraction ratios. It therefore appears that clearance technics dependent on the extraction of PAH by the tubules are valid measurements of renal plasma flow despite variation in oxygenation.

Tubular function is generally believed to be well maintained in heart failure, as manifested by the ability of the kidney to elaborate a concentrated urine[36] and by the normal extraction ratios. Heller and Jacobson cast doubt on this general impression by their observations that the maximum tubular excretory capacity for PAH (Tm_{PAH}) was reduced in heart failure and returned to normal with restoration of cardiac compensation.[23] They ascribed the reduction in Tm to the presence of anoxia.

We were able to determine the Tm_{PAH} successfully at various levels of oxygenation in 4 of our subjects (including 1 control and 3 with cor pulmonale, of whom 1 was in heart failure). The control values for all subjects obtained while they were breathing room air were within normal limits (77.5 ± 12.9)[37]; the Tm_{PAH} prior to the onset of heart failure in subject M. H. was not determined. There was no significant change in Tm_{PAH} in response to anoxia or increased arterial oxygen tensions. Scott and Elliott[27] have reported normal Tm_{PAH} in their chronically anoxic subjects with congenital cardiac disease. These combined observations suggest that the depression of Tm_{PAH} observed by Heller and Jacobson[23] in heart failure is probably not caused by anoxia per se. This preservation of tubular transport integrity during acute and chronic anoxia is of further interest because of the marked influence of anoxia on tubular enzyme systems in vitro.[38]

Diuresis[5] and oliguria[32] have been reported to occur during exposure to acute anoxia in man. The variable factors which influence the effects of anoxia on kidney function have been reviewed by Smith,[22] and include anxiety, degree and duration of anoxia, anesthesia, and other factors. The significance of these individual factors in the experiments reported from different laboratories cannot be evaluated. In our experiments, despite marked variation in oxygen tension, we could demonstrate no diuretic effect other than that due to water hydration during the study.

Albuminuria appeared in only 1 chronically anoxic subject with heart failure (A. D.) during the severe arterial oxygen desaturation caused by the inhalation of 16 per cent oxygen. Albuminuria did not appear in other subjects similarly exposed, despite more marked arterial oxygen desaturation. Whether the albuminuria in subject A. D. reflected increased capillary permeability (due to anoxia or increased intraglomerular pressure) or diminished tubular reabsorption of protein cannot be stated with certainty. The capillaries of the kidney are apparently well protected against damage by anoxia. The extreme venous oxygen desaturation required for capillary injury is prevented[39, 40] by the high oxygen environment of the kidney, which is in turn maintained by the low arteriovenous oxygen difference, polycythemia and increased renal blood flow. In our subject, A. D., albuminuria may reflect, perhaps in part, the failure of at least one of these compensatory mechanisms (renal hyperemia) to occur.

Summary

1. Renal function and sodium excretion were studied in two groups of patients with cor pulmonale; one group was in heart failure at the time of study and the other had recovered from at least one previous episode of heart failure.

2. As in subjects with heart failure of other etiology, renal plasma flow is characteristically reduced and the filtration fraction increased. The afferent arteriole is demonstrated to be the site of major segmental resistance to blood flow through the kidney during heart failure.

3. Persistent impairment of kidney function was present despite recovery from heart failure. The possible causes are discussed.

4. The acute aggravation and relief of an-

oxia were induced in order to investigate compensatory mechanisms which exist in these chronically anoxic subjects. Relief of anoxia depressed renal blood flow; increase of anoxia by means of gas mixtures low in oxygen content tended to increase renal blood flow. Sodium excretion paralleled renal plasma flow in direction but not in degree. Anoxia apparently plays little role in the genesis of heart failure.

5. The cardiac output contributes to but does not solely determine the blood flow through the kidney during variation in level of oxygenation. The renal response to anoxia is not mediated by epinephrine.

6. The renal extraction ratios for PAH were unchanged at the various levels of oxygenation, validating the use of PAH as a measurement of renal plasma flow under these conditions.

7. The Tm_{PAH} was not affected by change in level of oxygenation. The implications of this finding are presented.

8. Albuminuria appeared in 1 subject following severe arterial oxygen desaturation. The mechanisms by which the kidney adapts to chronic anoxia are discussed.

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Blood Pressure in the Unanesthetized Rat. I.

By Frederick Olmsted, A. C. Corcoran, M.D., and Irvine H. Page, M.D.

Methods of indirectly determining blood pressure in the rat are reviewed and their drawbacks noted. A new method is described which has the advantage of objectivity and provides permanent graphic record of each determination. The end point used is the reappearance of pulsation in the foot distal to a slowly deflating leg cuff. Application of the method is described and its use compared with tail plethysmography.

Of the many methods devised for the measurement of blood pressure in small animals, the most accurate is the high frequency manometer with arterial cannulation.[1] The necessary operative procedure and anesthetics may, however, disturb arterial pressure unpredictably, and such observations can not be repeated over long periods. Indirect methods have therefore been developed.

These are based on the detection of arterial inflow distal to a slowly deflating cuff on the foot, tail or ear of the animal. Thus Kunstmann[2] observed the color change in the foot as was described for the human finger by Gärtner.[3] Bonsman[4] utilized photoelectric transmittance of the rat tail. Moberg,[5] with a special viewing and occluding capsule, observed the resumption of the blood flow in the ear of anesthetized rats. Griffith[6] used as an end point the inflow in the capillaries of the interdigital web. This method was later used by Rubin,[7] Fasciolo[8] and Duncan.[9] Unfortunately, it requires both microscopy and anesthesia. A simpler but more traumatic method was used by Diaz.[10] This consisted of snipping a small piece of the tail and noting the appearance of blood flow at the wound as the occluding cuff pressure was lowered. The number of measurements possible is self limited.

Byrom[11] devised a sensitive water plethysmograph for use on the tail of the anesthetized rat. This instrument was modified for use in unanesthetized animals by Harrison, Grollman, and Williams,[12] Kempf and Page[13] and Sobin.[14] Electrical modifications were described by Skeggs and Leonards,[15] Friedman and Freed[16] and Grimson.[17] In one form or another this method has been widely used in the study of experimental hypertension in rats.

At normal room temperatures, tail arterial inflow is small, and caudal arterial pressure low, but with heating at about 40 C. for about 10 minutes, the tail artery dilates, its pressure rises to that in the femoral or carotid arteries, and the increased volume flow facilitates plethysmographic measurements. Thus Harrison, Grollman and Williams stated they used ambient temperatures, which increased rectal temperature to 40 C. Neuman, Proskauer, and Graef[18] have since shown, however, that such vigorous heating increases arterial pressure. To offset this disadvantage of body heating, Sobin and Landis[14] described a modification of the tail apparatus in which heat (40 to 42 C.) was applied to the tail only for 10 or 15 minutes. They did not describe the effect of such heating on body temperature. As we show below, it is appreciable.

Kersten and his co-workers,[19] using the plethysmographic principles of Hurthle, and Kunstmann[2] and Bonsman,[4] devised a photoelectric foot plethysmograph, an appropriate rat holder, and an accurate but fragile occluding cuff. Systolic flow was detected from an ammeter needle connected by a direct current amplifier to a phototube which received variations in transmitted light caused by volume change. The advantage of such measurements in the foot as compared to those in the tail, lies in the avoidance of heating.

A drawback in all those methods is the imprecision of the end point, which is easily obscured by animal movement. Another disadvantage is the tendency toward subjective errors, for the operator must at the same time

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control cuff pressure, observe its level and receive some signal of arterial inflow.

We therefore proposed to develop a procedure with a graphically recorded end point. The end point used was noted by Vierordt in the last century as the obliteration or return of pulse wave under proximal compression. In this report we shall describe this method, demonstrate its accuracy, and compare the results obtained with the results of tail plethysmography.

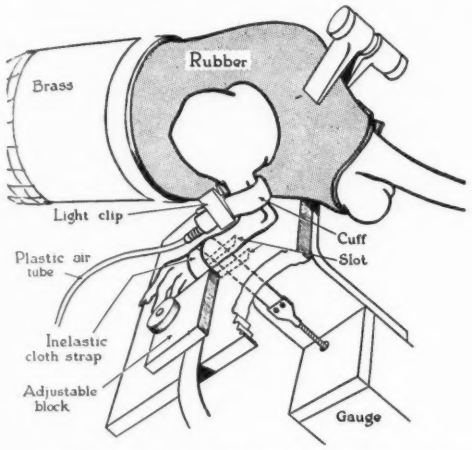

FIG. 1. Animal holder and strain gage. The holders were made in several diameters with the heavy wire mesh head restrainer sliding in the brass tube to fit the rat compactly.

METHOD

Three methods of detection of pulse wave were tested; the mechanical, the audiometric and one dependent on change of electrical impedance (Nyboer).[20] In the audiometric method used, artefacts of animal movement and microphone "noise" interfered seriously. Resistance changes due to animal movement, electrode contact change, and complexity of the apparatus are disadvantages of the impedance method. The mechanical transducer with vacuum tube amplification was therefore selected.

The pulse in the rat's foot can be detected by an unbonded strain gage bridge (Statham), and amplified output can be observed on a suitable oscillograph. Interferences from respiratory and animal movements make it desirable to record the output with a direct writing oscillograph, such as the Brush Penmotor, so that the characteristic rhythm of the pulse may be noted. Cuff pressure is simultaneously recorded on the paper trace. The record obtained is permanent and the measurements are truly objective. Rapid inflation and slow deflation of the cuff is made semiautomatic. The cuff used is not as exactly proportioned as that described by Kersten and co-workers[19] but it is rugged and can be rapidly applied.

The holder (fig. 1) is similar to that of Kersten and associates.[19] Rubber is used instead of leather for the flexible hind part. The animal's position is made horizontal, and an oil cloth strap applied over the lower leg is connected to the strain gage and acts both as pickup and foot restrainer. To facilitate placing the animal in a natural position, the lucite foot platform is mounted at an angle of 45 degrees on a heavy metal slab which may be moved horizontally to any position.

Since the foot pulse voltage from the gage is of the order of 30 microvolts, a high gain amplifier is connected to the gage output. The circuit used (fig. 2) gives a 3 cm. deflection for a 50 microvolt square wave input (a gain of 6×10^5). The frequency response to a sine wave falls off rapidly below 5 cycles per second and above 35 cycles per second. The apparatus responds to the rising systolic phase of the transmitted pulse and not to the pulse wave as a whole. The systolic signal in the rat has a duration of the order of one thirty-fifth of a second. The amplifying system is thus adapted to the signal desired, while other signals are to an extent obscured. Unblocking circuits are provided in the amplifier because of the surge currents caused by animal movement.

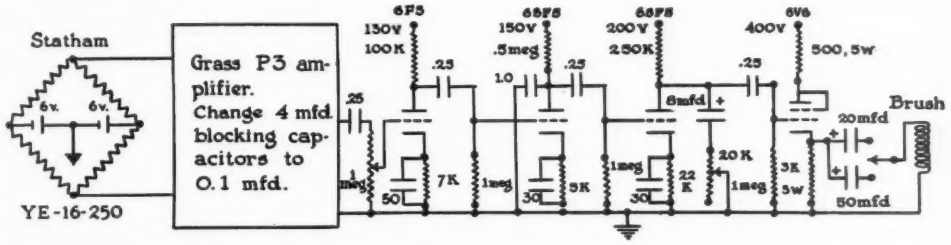

FIG. 2. Electronic circuit. More complicated systems with selective band filtering were tried and found unusable.

The pulse recorder is a Brush Penmotor mounted at one side of a standard two channel chassis. This provides an 8.5 cm. width for recording cuff pressure, and allows space for the cuff pressure recorder. This is a receptor Selsyn motor controlling a pen moving normal to the direction of the paper travel. The drive Selsyn motor is mounted separately from the Brush chassis and is activated by a 4 inch sylphon bellows opposed by a helical spring. The pressure range of bellows and spring is 0 to 250 mm. Hg. The motors are General Electric #2JIFI, 110 volt, 400 cycles per second, run by 25 volts, 60 cycles per second. The pen trace is calibrated by step pressure applied to the bellows.

The cuff consists of a 1 inch length of $\frac{1}{4}$ inch Penrose tubing, backed by a layer of heavy dental dam. Air is supplied through a length of fine plastic tubing. Air pressure is reduced from laboratory air lines and is controlled by a special valve (fig. 3).*

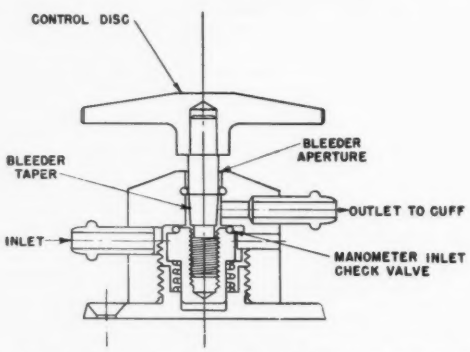

FIG. 3. Valve for inflation and deflation of cuff as described in text.

The action of this valve is such that pushing the control disc down inflates the cuff, and releasing it starts a gradual leak from the system, finely regulatable by rotation of the control disc. Two sphygmograms are shown in figure 4; *B* from a quiet animal, *A* from a more restless one. In spite of the restlessness and movements of the animal, and resulting dysrhythmic pen swings, the point of the pulse return is clear.

Satisfactory use of the method depends, as with other procedures, on practice and training of animals and operator. Proper adjustment of tension and placing of the foot strap are learned with practice. While useful records can often be obtained from untrained animals, their habituation to the procedure greatly speeds the reliability and rate of measurement. For clear recordings, the unanesthetized rat should be kept at about 30 C. for an hour or more.

* Construction by the MicroMetric Company.

ACCURACY OF METHOD

Seventy-five simultaneous direct Hamilton manometer and indirect foot pulse determinations were made under pentobarbital anesthesia and recorded photographically as in figure 5. The comparison of direct and indirect methods is graphed in figure 6, in which the 45 degree slope represents ideal correlation of methods. In the lower ranges (56 to 100 mm. Hg) indirect measurements indicate a lower pressure than direct, but in the higher ranges (130 to 180) there is a tendency toward the reverse. A similar

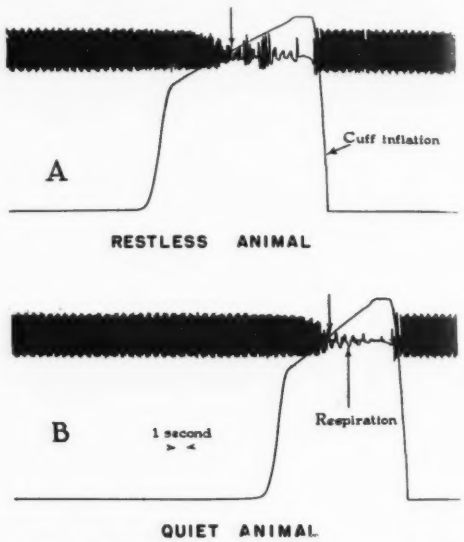

FIG. 4. Sphygmograms as described in text. Arrows directed downward mark systolic points.

swing about a point of maximum accuracy was noted by Hamilton[21] in comparing optically and plethysmographically recorded tail pressures. The average deviation from the mean carotid systolic pressure for the entire series is 5.6 mm. Hg.

COMPARISON WITH TAIL PLETHYSMOGRAPHY

A group of 10 adult rats, normal and hypertensive, whose pressures ranged from 122 to 216 mm. Hg, were kept in a room at 30 C. Pressure determinations were made daily for 10 days by tail plethysmography,[13] and by the present method. The daily measurements were made in

rapid sequence. The foot pulse record was made first. The animal was then preheated for three minutes at 45 C. and tail and body kept at 40 C. measurement used was the mean of two close sequential observations. With both methods, a considerable daily variation was noticed. A

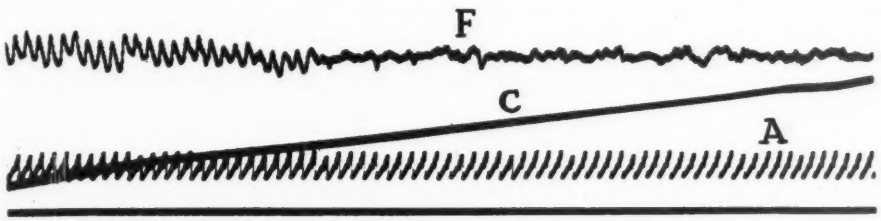

FIG. 5. Simultaneous optical tracings of indirect foot pulse (*F*) and cuff pressure (*C*) with direct intra-arterial pressure record (*A*) below.

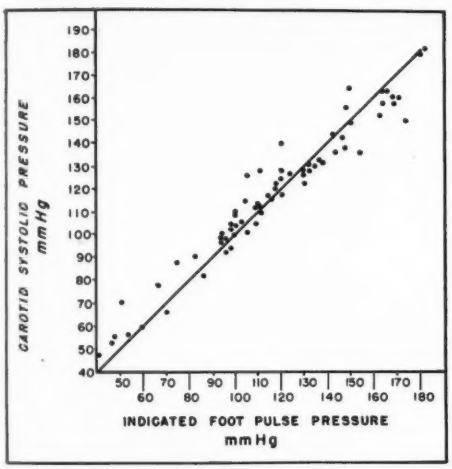

FIG. 6. Scattergram of indicated foot pulse pressures (abscissa) and optically recorded intra-arterial pressures (ordinate).

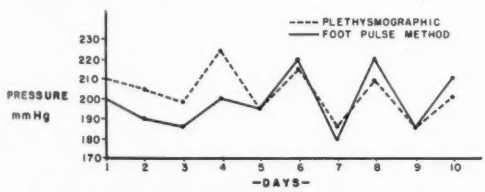

FIG. 7. Day by day variations of consecutive measurements by tail plethysmographic and foot pulse method.

during the tail plethysmography. The foot pulse pressure accepted was that recorded after pressure had stabilized for one minute. This level was usually lower than that recorded when the animal was first placed in the holder. The tail striking example of this is shown in figure 7. The mean of the 100 foot measurements was 158.3 mm. Hg ($\sigma = \pm 14.5$) and that of measurements from the tail, 166 mm. Hg ($\sigma = \pm 16.6$).

In comparison to tail plethysmography, foot pulse pressure records can be made at intervals as short as 10 seconds, and can be repeated for as long as the rat will tolerate restraint. The apparatus described above permits observation of concurrent changes in pulse and respiratory rates.

SUMMARY

A method is described for the graphic registration of systolic arterial pressure in unanesthetized rats. It depends upon detection and amplification of the mechanical pulse wave in the foot distal to an inflatable cuff, and simultaneous ink recording of pulse signal and cuff pressure. The method is compared with tail plethysmography, and no important difference of pressure found, although the electrical foot method has other inherent advantages.

The method is accurate and objective. Values obtained agree well with those found by foot plethysmography. Sequential determinations can be made at intervals of 10 seconds.

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Blood Pressure in the Unanesthetized Rat

II. Spontaneous Variations and Effect of Heat

By Frederick Olmsted, A. C. Corcoran, M.D., and Irvine H. Page, M.D.

Heating is commonly used in indirect determinations of blood pressure in the rat. Its effect on arterial pressure is determined at short sequential intervals by a method which permits rapid measurements. Spontaneous variations in the rat's blood pressure are noted and analyzed. A plan is suggested which minimizes the effect of these variations by setting up criteria of significance of blood pressure change as between control and experimental periods.

ESTIMATES of the normal rat's blood pressure have varied widely from one laboratory to another. Arterial pressure is variously stated to be consistent from day to day, or to extend over a wide range. Most determinations are made by procedures in which the animal is heated in various ways.

Our purpose is to describe the effect of heating on the blood pressure of intact, unanesthetized rats as determined by an objective method.[1] We have also analyzed day to day fluctuations of blood pressure in these animals.

I. Effect of Heating

Method

A group of 10 rats, normal and hypertensive, whose control pressures by the foot pulse method ranged from 80 to 172 mm. Hg were maintained in a room at 30 C. The control levels of pressure at 30 C. were recorded from readings which had stabilized for at least one minute. The animals were then heated by a gentle current of air, electrically warmed and thermostatically controlled. For tail heating alone, the tail was placed in an electrically warmed tube maintained at 45 C. Rectal temperatures were measured with a thermocouple thermometer.

Three schedules of warming were tested. In one, 45 C. heat was applied for 10 minutes. The second simulated the plethysmographic routine of this laboratory, where rats are preheated at 45 C. for three minutes, and then placed in a tail plethysmograph apparatus at 40 C. The third followed the Sobin procedure in which the tail only is warmed for 15 minutes at 45 C.

Results

Blood pressures were recorded at 30 and rectal temperatures at 60 second intervals. Minute by minute averages for these functions are shown in figure 1. Pulse rates were determined from the recordings of the 45 C. group. They did not correlate with changes in blood pressure or body temperature.

The rats heated at 45 C. for 10 minutes exhibited a steady rise in blood pressure. At 10 minutes the mean increment was 42 mm. Hg (+ 33 per cent of the control mean). Those heated at 45 C. for three minutes and then at 40 C. attained a pressure rise of 20 mm. Hg after the three minutes at 45 C., which is equal to the increase in the 45 C. group at this time. Pressure stabilized at about this level during exposure to 40 C. Those animals whose tails only were heated for 15 minutes at 45 C. exhibited a similar slow rise. In 15 minutes they attained about the same pressure levels as the second group. Most of the pressure rise in the tail-heated series occurred in the first six minutes.

To compare effects of heating in normotensive rats, the animals heated at 45 C. were divided into two groups. One group had control readings below 120 mm. Hg (averaging 100) and the other had control determinations above 140 mm. Hg (averaging 158). The average rises in each group are graphed in figure 2. The increment in the normotensive group at 10 minutes is 49 mm. Hg (+ 49 per cent), that of the hypertensive group is 40 (+ 25 per cent). For the first three minutes, the normotensive group increased 25 and the hypertensive 10 mm. Hg. The increase of pressure caused by heating was consistently less in hypertensive than in normal rats.

It was observed that during heating runs, the amplification could be gradually reduced

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several fold without decreasing the amplitude of the recorded pulse stroke. This is interpreted as evidence of arterial vasodilation in the foot.

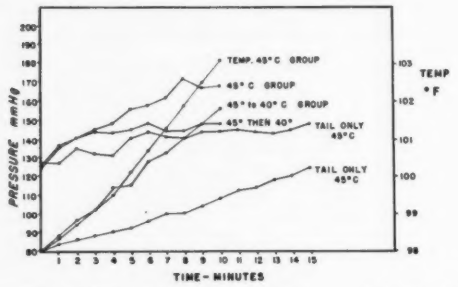

FIG. 1. Comparison of foot pulse recorded arterial pressures (left ordinate) at one-minute intervals (abscissa) in groups of rats heated by methods noted in text to various levels of rectal temperature (right ordinate).

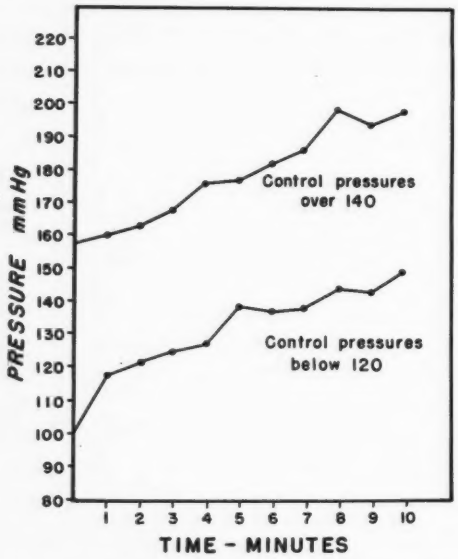

FIG. 2. Comparison of mean effect of heating on arterial pressure in normotensive and hypertensive groups.

II. VARIABILITY OF ARTERIAL PRESSURE

Method

Ten normal rats weighing from 125 to 175 Gm. were housed at 30 C. Blood pressure measurements were made by the foot pulse method daily for 10 days. Values recorded were those measured after the pressure had stabilized for at least one minute.

Results

The range of pressure recorded was from 70 to 175 mm. Hg. The mean of the 100 determinations was 114 mm. Hg. The standard deviation for the group was ±16.3 mm.

Similarly, the pressures of 7 hypertensive rats whose group average was 184 mm. Hg ranged from 100 to 228 mm. Hg. The standard deviation was ±17.1 mm. Hg.

Day to day fluctuations apart, animals recently handled or inadequately habituated to the apparatus commonly show rapid variations of as much as 30 mm. Hg. These changes take place in a few seconds and emphasize the desirability of the repetition of observations in the selection of base line for blood pressure study.

TABLE 1.—*Solutions of Equation 2 for Groups of Varying Size, Observed Daily for Five Days*

Difference between average pressure of two groups (*mm. Hg*)	Minimum number of animals per group for significant data
5	42
10	11
15	5
20	3
25	2
30	2

DISCUSSION

Effect of Heating

Our data confirm the tail plethysmograph observations of Proskauer, Neumann and Graef,[2] and extend them by demonstrating the sequence and regularity of pressure change in heated rats. The need for systematic control of heating technics is apparent. When conditions are closely controlled, such methods can yield useful comparative values, since the sequence of heat-induced pressure change in a group is regular. Measurements made after heating the tail at 45 C. for 15 minutes and those obtained by our more convenient plethysmographic routine are substantially the same.

We have no adequate explanation of the rise in blood pressure which results from heating in rats. Heating has been observed to cause renal vasoconstriction in man.[3, 4] During heating the

increased peripheral blood flow must be provided for by splanchnic vasoconstriction, increased cardiac output, or both. The absence of a relationship between pulse rate and blood pressure change might suggest that in the rat splanchnic vasoconstriction is the principal cause of the pressure rise. However, since cardiac output is a function of metabolic rate, and the rat is known to alter metabolism with shifts of external temperature away from 28 or 29 C.,[5] the pressure rise may be cardiogenic. The proportionally smaller and slower rise of pressure in hypertensive as compared to normal rats is of interest since it suggests that the pressor mechanisms which operate during heating are either less responsive in renal hypertension or already submaximally engaged.

The day to day variability of pressure in the rat imposes a certain requirement as to the number of animals and successive daily measurements needed to obtain significant data. When the standard deviations of each animal in the groups of normal or hypertensive rats are graphed against duration of measurement in days, it is evident that the variability does not diminish after five successive days in groups of four or more. Seventeen mm. Hg can be taken as the usual variability of the rat's blood pressure.

The standard deviation of the difference between the averages of two groups is equal to

$$\sqrt{\frac{(\sigma \text{ control group})^2}{n-1} + \frac{(\sigma \text{ experimental group})^2}{n-1}} \quad (1)$$

$$\text{or } \sqrt{\frac{2(17)^2}{n-1}} \text{ or } \sqrt{\frac{578}{n-1}} \quad (2)$$

where n = number of determinations.

For a probability of 500 to 1 that a difference between the arithmetic means of pressures of two groups of animals is significant, this difference should be equal to or greater than three times the standard deviation of the difference. In table 1 is shown the solution of equation 2 (after five successive daily determinations) for the differences of the averages of pressures, in two groups. Obviously, a 5 mm. Hg pressure change, to be significant, requires an impractical number of animals. However, the group size is reasonable for the difference of 10 mm.

Summary

1. The effect of various modes of heating on the graphically recorded blood pressure of the rat is regularly and sequentially pressor in proportion to the amount of heating applied.

2. Careful control of the warming of rats in blood pressure determinations which involve heating is essential for accuracy.

3. The occasional rapid variability of the rat's blood pressure is noted. The day to day variations are analyzed to determine a minimum experiment group for five successive daily measurements.

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The Initial Vibrations of the First Heart Sound

By Timothy Counihan, M.D., Addison Lee Messer, M.D., Maurice B. Rappaport, E.E., and Howard B. Sprague, M.D.

The major component of the normal first heart sound is that due to valvular closure. Preceding this there occur low frequency, low amplitude vibrations commonly attributed to auricular systole. It has been shown in this study that such vibrations appear invariably even though the auricles are fibrillating, and in heart block when auricular systole is widely seperated from ventricular systole. It is concluded that the onset of ventricular contraction itself causes these vibrations through mechanisms unrelated to auricular contraction, and prior to the valvular component.

THE HEART sounds, suitably recorded, yield most important information on the sequence of mechanical events that comprise the cardiac cycle. It is essential then that each component group of vibrations of the heart sounds be exactly attributed to the precise mechanical event leading to its production. This paper deals with the first component of the first heart sound and its probable mode of origin, that is, with those few vibrations of low frequency and low amplitude that initiate the first sound.

The first heart sound is composed of vibrations of diverse frequency and amplitude occurring at the onset of ventricular systole. Caeiro and Orias,[1] on the basis of a phonocardiographic study of 20 healthy medical students, divided these vibrations into four component groups. The first of these groups they assumed to be the terminal vibrations associated with auricular systole and termed it the auricular component of the first heart sound. These low frequency, low amplitude vibrations bear a temporal relationship to the P wave of the simultaneously recorded electrocardiogram that is consistent with that of the auricular sound when this is dissociated from ventricular contraction, as in complete or partial heart block. In a phonocardiographic analysis of the normal heart sounds by two of us (Rappaport and Sprague)[2] this interpretation of the origin of the first component of the first sound was accepted; Luisada, Mendoza and Alimurung[3] also are in agreement. However, on the basis of further observations, as described below, we feel that a modification of this interpretation is necessary.

Phonocardiograms recorded at the cardiac apex of 28 patients with auricular fibrillation and 2 with complete heart block were studied with respect to the initial vibrations of the first sound. All recordings were made with a Sanborn Tribeam phonocardiograph. The electrocardiogram and apex cardiogram were recorded simultaneously for reference. Vibrations of low frequency and low amplitude were present at the beginning of the first heart sound in all of the cases with auricular fibrillation (fig. 1, *bottom*) and in the 2 cases of complete heart block, even when auricular systole preceded ventricular systole by an interval sufficient for the auricular sound to have expended itself (fig. 1, *top*). The average duration of this group of vibrations was 0.05 second, with a range of 0.03 to 0.06 second, and the average frequency was 35 cycles per second, with a range of 20 to 60 double vibrations.

These values must be interpreted in the light of the technic employed in making the records as described by Rappaport and Sprague in a previous communication[4]: the *stethoscopic* and *logarithmic* microphones were employed in all the cases studied. Although the stethoscopic microphone registers low frequency vibrations more efficiently, the initial first heart sound

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This work was done while one of us (T.C.) was on Research Grant from the Medical Research Council of Ireland.

vibrations, however, lie within the frequency range of human audibility and are well registered with the *logarithmic* microphone (fig. 1). They start after the beginning of the QRS complex in the electrocardiogram, which is recorded simultaneously, and with or shortly after the beginning of the rise of the first positive systolic wave in the apex cardiogram.

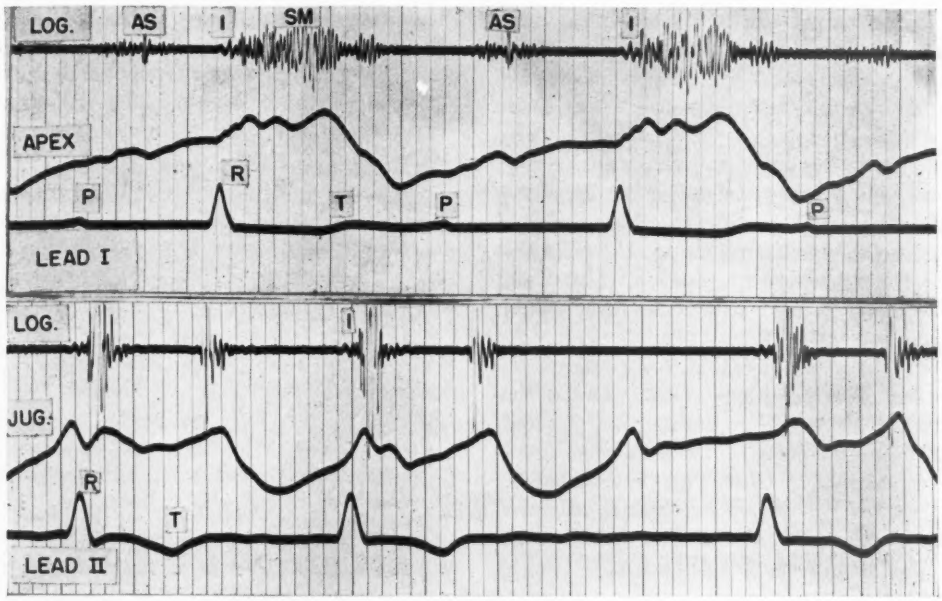

FIG. 1. Phonocardiograms recorded with logarithmic microphone. *Top:* Complete heart block. Heart sounds at apex with apex cardiogram and electrocardiogram. AS = auricular sound. SM = systolic murmur. The numeral 1 refers to the first component of the first heart sound. *Bottom:* Auricular fibrillation. Heart sounds at apex with jugular pulse and electrocardiogram. The numeral 1 refers to the first component of the first heart sound.

DISCUSSION

There is no question that vibrations of auricular origin can frequently be recognized in phonocardiograms, following the P wave and preceding the onset of the QRS complex, and such vibrations maintain their time relationship with the P wave when the P-R interval changes. However, the initial low frequency, low amplitude vibrations of the first sound that succeed the beginning of the QRS do not bear such relationship to auricular systole, occurring even in its absence. On the other hand, they do show a constant relationship to the main vibrations of the first sound that form its second component, and if we accept, as the evidence would indicate, that the beginning of the *main* vibrations (that is, second component) of the first sound marks closure of the auriculoventricular valves,[5] then the initial low frequency, low amplitude vibrations (that is, first component) occur during the pre-isometric phase of ventricular systole. Again, the initial group of vibrations coincides with, or follows immediately after, the beginning of the systolic impulse of the apex cardiogram. These observations are consistent with the earlier suggestion of Wiggers[6] that "when the ventricle begins its contraction, its position changes slightly. This may produce the first feeble vibrations of the first sound." More recently this author[7] has accepted the explanation of Caeiro and Orias[1] of the atrial origin of these preisometric vibrations of the first heart sound. However, he pointed out[6] that while these

sounds begin definitely before the rise of intraventricular pressure, they may continue slightly into the early period of rising tension and those vibrations which do continue represent initial vibrations of the first ventricular sound rather than the termination of the atrial sound.

It is apparent that the vibrations we have described occur with the beginning of ventricular contraction and truly constitute the first component of the first heart sound. They are associated with the development of tension in the ventricular muscle fibers which initiates the rise of intraventricular pressure. Since these vibrations occur before the main group associated with closure of the A-V valves, they must be due directly to slight shortening of the muscle fibers initiating the rise of intraventricular pressure, or to the taking up of slack in the valve leaflets before they become opposed, or, conceivably, to movement of the heart within the thorax.

We feel that in the majority of instances vibrations of atrial origin, which precede the beginning of ventricular contraction, can and should be differentiated from the first heart sound and that the term "first component of the first heart sound" should include only the initial low frequency vibrations associated with the beginning of ventricular systole.

Conclusion

1. An initial group of low frequency, low amplitude vibrations of the first heart sound can be recorded in the absence of effective auricular contraction.

2. The evidence indicates that they are produced during the pre-isometric phase of ventricular systole.

3. In normal individuals the initial vibrations of the first heart sound are related to the main vibrations of the first sound rather than to auricular systole, suggesting that they are of the same origin as those that occur in the absence of pertinent auricular contraction.

4. These findings do not apply to the auricular origin of those vibrations that precede the beginning of the QRS or vary with the P-R interval.

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The Q-T Interval in Chronic Cor Pulmonale

By James K. Alexander, M.D., M. Irené Ferrer, M.D., Réjane M. Harvey, M.D., and André Cournand, M.D.

In 13 patients in whom the diagnosis of chronic cor pulmonale was made after careful physiologic studies, the Q-T interval was found to be within normal limits regardless of the presence or absence of cardiac failure. The finding is in sharp contrast to the prolongation of this interval in the more common types of heart disease, as exemplified by a group of 14 patients with hypertensive and arteriosclerotic heart disease. Measurement of the Q-T interval therefore may be useful in differentiating pure chronic cor pulmonale from other types of heart disease with congestive failure.

ALTHOUGH there has been much consideration in the past given the duration of the Q-T interval in the electrocardiogram, more recently attention has been directed with renewed interest toward its possible diagnostic significance in various clinical conditions. It seems to be generally agreed that the Q-T interval represents the period of depolarization and repolarization of the ventricular muscle, and that normally there is variation in its length, dependent upon age, sex, and heart rate. The primary factors actually determining its duration in normal and pathologic states, presumably inherent in muscle metabolism, await further elucidation.

It is known, however, that the duration of the Q-T interval may be shortened by digitalis administration,[5, 18] hypercalcemia[23] and vagal stimulation.[15] It may be prolonged in association with changes in position,[22] myocardial infarction,[1, 18] cardiac enlargement,[6] congestive heart failure of varied etiology,[7, 25] hypopotassemia,[13, 14] hypocalcemia,[14, 18, 23] and administration of certain drugs such as quinidine,[28, 29] atropine[15] and adrenaline.[15] The concept that the Q-T interval is often prolonged beyond the upper limit of normal with acute rheumatic carditis[12] has recently been challenged,[10] as has the contention[26] that greater muscle mass causes lengthening.[15] The relationship between the Q-T interval and the duration of mechanical systole is inconstant,[23, 24] and the use of the term "electrical systole" to describe the Q-T interval seems, therefore, unjustified, particularly since the conduction phenomena associated with depolarization and repolarization are in no way analogous to actual mechanical contraction.

The present study was undertaken to determine what alterations in Q-T interval, if any, might be found in association with chronic cor pulmonale, since this latter has not been previously mentioned in the literature and in view of the changes observed in the duration of the Q-T interval in other types of heart disease.[6, 7]

Material and Methods

All 13 cases of chronic cor pulmonale reported in this study fulfilled the accepted criteria for the diagnosis,[30] namely the presence of chronic pulmonary disease, evidence of right heart enlargement or failure, marked cyanosis, and no other demonstrable etiology of their heart disease. Most of these patients have been reported in a previous paper[20] with physiologic studies to confirm the clinical diagnosis, and in all instances actual measurements indicated the presence of pulmonary insufficiency, pulmonary hypertension, arterial unsaturation and polycythemia. Three patients (L. P., L. B., and T. D.) had been in congestive failure recently but were not in failure at the time of study, and a fourth (J. McC.) had never been in failure. The remainder had clinical evidence of failure, and the

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hypervolemia and elevated mean auricular and right ventricular end diastolic pressures characteristic of right heart decompensation. All patients had normal sinus rhythm or sinus tachycardia by electrocardiogram, and had received no digitalis or other cardiac drug prior to study.

Q-T measurements were made in the usual manner (from the beginning of the initial deflection in the QRS complex to the end of the T wave at its return to the isoelectric line) in each lead of the twelve or fourteen lead electrocardiogram (standard leads I, II, III, aV_R, aV_L, aV_F, V_1 through V_6, V_{3R}, V_{4R}) and these results averaged to give the "average Q-T" for the individual patient at his heart rate. There were fewer measurements in some instances due to the absence of clear demarcation of the T wave or technically unsatisfactory tracings, and an average value is reported for each patient. Cycle length was taken as the average R-R interval, measured as the distance between peaks of successive R waves, for 10 cycles. Calculation of K in Bazett's formula[11] ($Q\text{-}T = K\sqrt{\text{cycle length}}$) was done by the slide rule method.[8]

The 14 cases of hypertensive cardiovascular disease and arteriosclerotic heart disease whose Q-T intervals were chosen for comparison with the patients having chronic cor pulmonale, had, in addition to the usual clinical findings of left ventricular or left and right heart failure, physiologic studies confirming the presence of these forms of decompensation according to previously published criteria.[19] Again the rhythm was normal sinus, and no digitalis preparations or other drugs had been administered prior to study. Q-T interval measurements were done as described above.

TABLE 1.—*The Q-T Interval in Thirteen Patients with Chronic Cor Pulmonale*

Patient	Sex	Heart Rate	Aver. Q-T (sec.)	Upper Limit of Normal Q-T (sec.)	K	Upper Limit of Normal for K		
						B	CL	SH
A. P.	M	96	0.332	0.344	0.421	0.392	0.400	0.433
L. P.	M	83	0.303	0.368	0.357			
T. D.	M	93	0.300	0.351	0.375			
B. B.	M	107	0.259	0.328	0.346			
T. A.	M	100	0.295	0.338	0.381			
J. B.	M	100	0.308	0.338	0.398			
L. B.	M	85	0.338	0.363	0.404			
F. C.	M	66	0.343	0.404	0.362			
M. V.	M	59	0.390	0.425	0.387			
J. McC.	M	110	0.285	0.325	0.388			
F. E.	F	88	0.342	0.359	0.415	0.440	0.421	0.456
A. D.	F	90	0.328	0.364	0.404			
B. B.	F	110	0.295	0.325	0.402			

In this table "Aver. Q-T" indicates the actual measured average Q-T interval, and "K" the actual value of K calculated from Bazett's formula. "Upper Limit of Normal Q-T" is the upper limit of normal for duration of the Q-T interval at the given heart rate in each patient as cited by Ashman and Hull. "Upper Limit of Normal for K" refers to the upper limit for K for normal males and females according to the data of Bazett (B), Cheer and Li (CL), and Shipley and Hallaran (SH) respectively. See text.

RESULTS

The results of the Q-T measurements in 13 cases of cor pulmonale are summarized in table 1. It will be seen that in every instance the measured average Q-T duration for the given heart rate is below the upper limit of normal cited in the data of Ashman and Hull.[18] The actual value of K is either below or at the normal upper limit in all instances except one using the criteria of Bazett[11] and Cheer and Li,[17] and in every instance, according to the criteria of Shipley and Hallaran.[21] The average values for K in the 10 males (0.382) and three females (0.407) used in this study are both well below the upper limits of normal cited by all three sources. In males

TABLE 2.—*The Q-T Interval in Fourteen Patients with Hypertensive Cardiovascular Disease and Arteriosclerotic Heart Disease*

Patient	Sex	Type Failure	Heart Rate	Aver. Q-T (sec.)	Upper Limit of Normal Q-T (sec.)	K	Upper Limit of Normal for K		
							B	CL	SH
N. P.	M	L & R	100	0.308	0.338	0.398	0.392	0.400	0.433
C. G.	M	L & R	120	0.308	0.310	0.436			
M. R.	M	L & R	107	0.340	0.325	0.455			
J. B.	M	L	100	0.346	0.338	0.447			
G. R.	M	L	130	0.336	0.294	0.496			
P. A.	M	L & R	73	0.400	0.384	0.442			
T. B.	M	L	75	0.389	0.384	0.436			
J. M.	M	L & R	115	0.330	0.317	0.457			
V. B.	M	L	78	0.347	0.378	0.399			
J. S.	M	L & R	83	0.378	0.368	0.446			
J. S.	M	L	83	0.394	0.368	0.465			
S. F.	F	L & R	65	0.430	0.418	0.448	0.440	0.421	0.456
I. J.	F	L	97	0.361	0.353	0.459			
D. M.	F	L & R	65	0.424	0.418	0.443			

For symbols see table 1. "Type Failure" refers in this table to the presence of left-sided (L) or left and right-sided (L and R) congestive failure. See text.

with chronic cor pulmonale, the average value of K in the 6 patients with cardiac failure (0.382) is the same (0.381) as in the 4 patients (L. P., T. D., L. B., J. McC.) who were compensated.

For the purpose of comparison, the Q-T measurements in 14 cases of hypertensive cardiovascular disease and arteriosclerotic heart disease in failure are tabulated in table 2. Here the measured Q-T is greater than the upper limit of normal in all but 3 instances according to the data of Ashman and Hull. A further demonstration of this is shown in figure 1 where the measured Q-T interval is plotted against heart rate in the cases of chronic cor pulmonale and hypertensive cardiovascular disease and arteriosclerotic heart disease. The observed values are plotted in relation to the predicted upper limit of normal,[18] which appears as a reference line. The values in chronic cor pulmonale are within normal limits and tend to fall well below those in hypertensive cardiovascular disease and arteriosclerotic heart disease, the majority of which are grouped above the upper limit of normal. The calculated values for K in the patients with hypertensive and arteriosclerotic heart disease (table 2) are above the upper limit of normal in every instance, according to Bazett's criteria, in all but 2 borderline

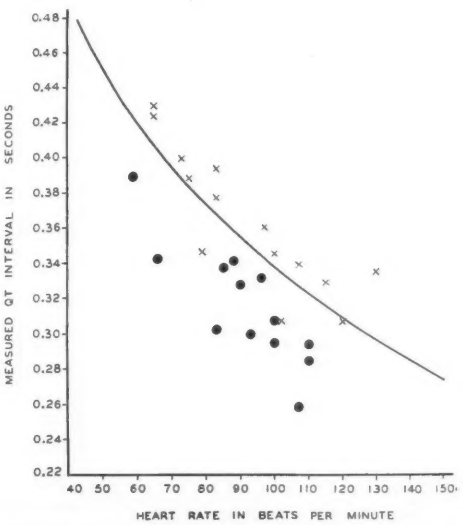

FIG. 1. The Q-T interval in patients with chronic cor pulmonale compared with patients with hypertensive and arteriosclerotic heart disease. The reference line here represents the predicted upper limit of normal for the measured Q-T interval in seconds at various heart rates, according to the data of Ashman and Hull. Closed circles represent the measured values for the Q-T interval in patients with chronic cor pulmonale and the crosses indicate the values in patients with hypertensive and arteriosclerotic heart disease.

instances, according to those of Cheer and Li, and in all instances but 4, according to those

of Shipley and Hallaran. In contrast to the results in cases of chronic cor pulmonale, the average values for K in males (0.434) and females (0.450) are either above or at the upper limits of normal cited by the three quoted sources. It may be of interest to note that the average value for K in males with left sided heart failure alone (0.449) appears to be somewhat higher than that in males with both left and right sided failure (0.439).

Discussion

Although this report is based on a small series of cases, the diagnosis of chronic cor pulmonale was clearly established in each instance and well documented with physiologic studies. The data obtained are open to only one interpretation, namely that with regard to the four sources of normal values quoted, the Q-T interval in chronic cor pulmonale is within normal limits both in patients with or without congestive failure. In addition, the value of K in this series is the same regardless of cardiac decompensation.

On the other hand, as might be expected on the basis of previous similar studies, Q-T measurements in patients with hypertensive cardiovascular disease and arteriosclerotic heart disease in cardiac failure were found to be prolonged beyond the upper limit of normal in the majority of cases.

The explanation for the absence of Q-T interval prolongation in chronic cor pulmonale cannot be given with certainty at this time. However, the evidence accumulated to date in this laboratory indicates that the burden in chronic cor pulmonale is on the right heart with resultant hypertrophy and dilatation on that side, and sparing of the left heart.[20] Since the levocardiogram is said to account for approximately 60 per cent of the total potential differences in the electrocardiogram, potentials originating entirely in the dextrocardiogram are therefore less readily manifest, and changes in the Q-T interval of the right heart, if present, might perhaps not be readily appreciated in the completed electrocardiogram.

The finding of a definite prolongation of the Q-T interval in the patients with hypertensive and arteriosclerotic heart disease is in accord with previous reports.[6, 7] The literature, however, contains no specific information as to the Q-T interval in patients with chronic cor pulmonale. The finding of a normal Q-T interval in such patients, as demonstrated by this study, is in sharp contrast to the findings in the more common forms of heart disease. Thus the duration of the Q-T interval may be a diagnostic aid in differentiating pure chronic cor pulmonale from other types of heart disease resulting in congestive failure. When chronic cor pulmonale exists in association with another form of cardiac disease, such as arteriosclerotic heart disease, the Q-T interval may be prolonged.[20, 27]

Summary and Conclusions

1. Measurements in 13 cases of chronic cor pulmonale with or without cardiac failure indicate that the Q-T interval is not prolonged in this condition.

2. Fourteen cases of hypertensive cardiovascular disease and arteriosclerotic heart disease in failure studied for comparison showed prolongation of the Q-T interval, as might be expected on the basis of previous reports.

3. It is suggested that measurements of the Q-T interval may be used as a diagnostic tool to aid in differentiating pure chronic cor pulmonale from other types of heart disease resulting in congestive failure.

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Retrograde Conduction from Premature Ventricular Contractions, a Common Occurrence in the Human Heart

By Albert D. Kistin, M.D., and Milton Landowne, M.D.

On the basis of studies of esophageal electrocardiograms the authors conclude that retrograde conduction to the atria from premature ventricular beats is common and that the theory of normal unidirectional block in the A-V node is not tenable. In most of the cases with retrograde conduction, the latter is not discernible in simultaneously recorded lead II, which explains why the phenomenon has previously been considered rare. Observations on the ventriculoatrial conduction time and the compensatory pause are presented. In two of the cases there are two orders of magnitude of ventriculoatrial conduction time, which, the authors postulate, may be due to two separate pathways of retrograde conduction.

RETROGRADE conduction to the atria from premature ventricular contractions is generally believed to be rare in the human,[8, 10, 11, 14, 19, 20, 22] although Ashman and Hull[2] state that they have observed this phenomenon repeatedly. We studied the esophageal leads of 33 individuals with premature ventricular beats and believe there is evidence of retrograde conduction in 15. These include cases in which there was no evidence of heart disease as well as cases of heart disease and cases in which the premature beats may have been related to the use of digitalis. The esophageal leads were recorded simultaneously with lead II in 12 of the 15 cases and in most of these the retrograde conduction, apparent in the esophageal leads, is difficult or impossible to recognize in lead II. Little attempt has been made to use this technic in the past. Brown[6] showed that retrograde P waves could be discerned in esophageal leads. Kline, Conn and Rosenbaum[15] used esophageal leads to demonstrate ventriculoatrial conduction in a case of complete atrioventricular block; at one time they could demonstrate the retrograde conduction in the esophageal leads but not in the simultaneously recorded standard leads.

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From the Cardiovascular Research Unit, Veterans Administration Hospital, Washington, D. C.

Technic

For esophageal exploring electrodes a modified Nyboer tube* was used consisting of rings of Monel metal about 5 mm. in diameter and 3 to 5 mm. long mounted on a soft rubber tube. The optimum position of the esophageal exploring electrode was determined in each case by trial, or several esophageal leads were recorded. The positions of the exploring electrodes in centimeters from the nares are designated by the numbers following the E in the figures. The esophageal and precordial exploring electrodes were paired with the Wilson indifferent electrode. A standard recording speed of 25 mm. per second was used so that the smallest time intervals on the illustrations represent 0.04 second. All records were taken with amplifier type instruments. A Technicon three channel electrocardiograph was used for the simultaneous tracings. The width of the record has been reduced for some of the illustrations without altering the alignment. For the records of single leads, the Sanborn Cardiette or Viso-Cardiette was used. An electropositive potential at the precordial and esophageal electrodes was recorded as an upward deflection.

* Manufactured by C. R. Bard Co., New York, N. Y.

There was no deliberate selection of cases available for study. As we became interested in the problem, we attempted to record esophageal leads in all cases showing numerous premature ventricular contractions. In this sense our material is a random series from a hospital population. In a few cases esophageal leads had already been recorded for other purposes and incidentally showed premature ventricular contractions. In some cases satisfactory esophageal leads could not be obtained.

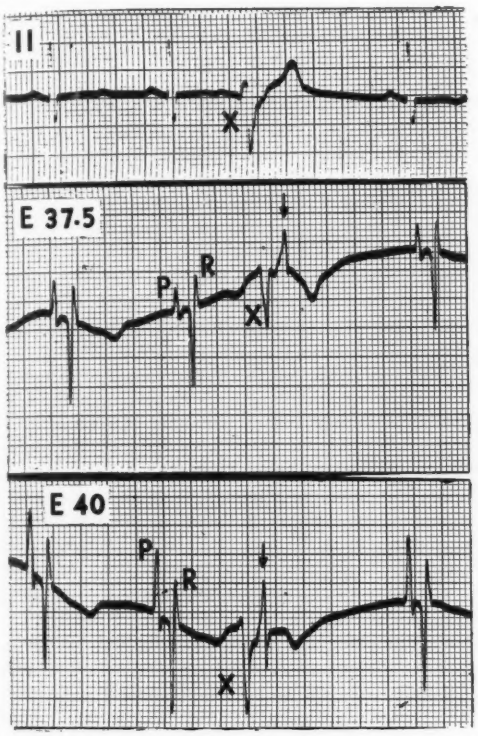

FIG. 1 (Case 11, table 1). Lead II and esophageal leads. X = premature ventricular contraction. The arrows point to the P waves produced by retrograde conduction. These differ in contour from the sinus P waves and occur prematurely with respect to the expected sinus P wave. (Some of the rapid deflections were retouched for illustration.)

Criteria of Retrograde Conduction

In esophageal leads from atrial levels there are large characteristic P waves with a rapid negative intrinsic deflection. Differences in direction of the atrial excitation wave may produce change in contour which may be minimal or not discernible in other leads. Furthermore the sharp positive peak of the esophageal P wave furnishes a precise reference point for timing from one P wave to another, even frequently when the latter are superimposed upon QRS or T.

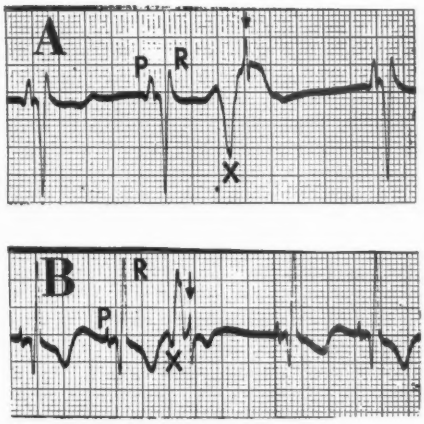

FIG. 2. Esophageal leads (*A* = E40, *B* = E42.5). X = premature ventricular contraction. The arrows point to retrograde P waves (P′). These differ in contour from the sinus P waves. In 2*A* (Case 15) the retrograde P is also premature with respect to the expected sinus P. The P′-P interval is longer than the preceding P-P. In 2*B* (Case 10) the P following the premature ventricular contraction is not premature and is probably due to fusion of retrograde activation and antegrade atrial activation from the S-A node.

The characteristics of P in the esophageal leads which we observed in these cases and which we interpret as due to retrograde conduction are: (1) it may differ from the sinus P waves in contour; (2) it may be premature with relation to the expected P wave of sinus origin, and in these instances it is followed by an interval to the next sinus P wave which is longer than the usual sinus P-P interval and which may or may not be compensatory; (3) it occurs within a limited range of time following the premature QRS. Not all the criteria are demonstrable in each case. Retrograde P waves superimposed on QRS and T may show a definitely premature peak although the superim-

position makes contour analysis difficult or impossible. In cases of fusion beats, that is, combinations of retrograde activation and antegrade activation from the sinus node, the contour of the P following the premature QRS considerably deeper negative deflection below the baseline than the sinus P waves.

In the esophageal leads the retrograde P need not be inverted or opposite in direction to the P of sinus origin, although the latter

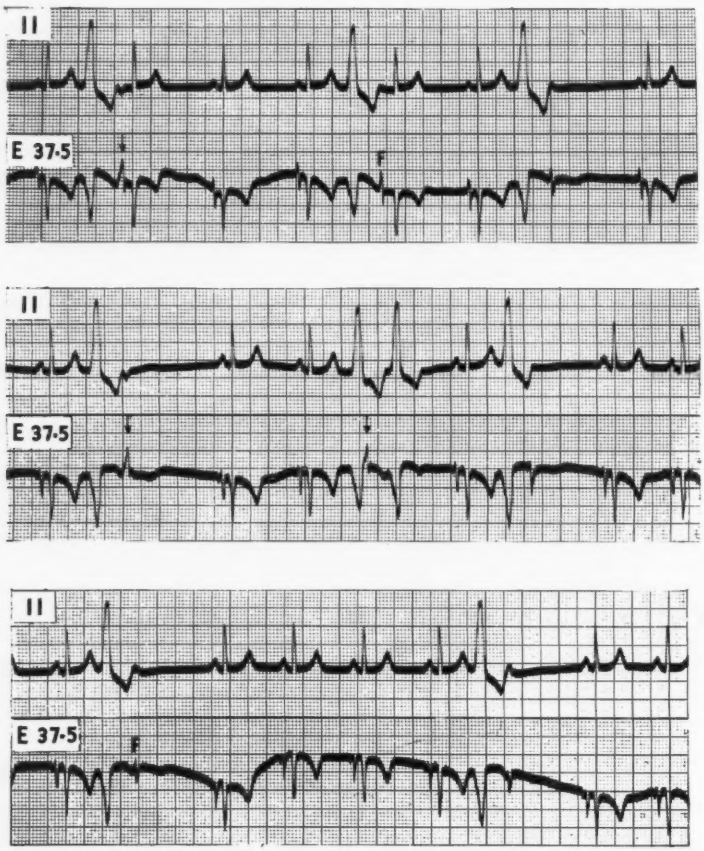

FIG. 3 (Case 4, table 1). Three sections of simultaneously recorded lead II and an esophageal lead. The arrows point to retrograde P waves. F = fusion P waves. Some of the other P waves following premature ventricular contractions are also possibly fusion P waves. Sometimes a distinct sinus P wave occurs following a premature ventricular contraction before retrograde activation becomes effective (last premature complex, middle tracings).

may be quite distinctive, yet the peak of the P wave may not be premature.

Contour. Retrograde P waves differing in contour from the sinus P waves are illustrated in figures 1 to 6. In figures 1, 4, and 5, the upstroke of the retrograde P is slower than that of the sinus P. In the 40 cm. lead of figure 1 and in figure 6 the retrograde P has a

may occur. The exploring electrode of a "unipolar" esophageal lead properly placed is close to the atrium and therefore a semidirect lead. An electropositive deflection will be recorded whenever the mean direction of the excitation wave is approaching the electrode, regardless of the origin of this approach. The steep negative or "intrinsic" deflection starting from the

positive peak of P represents the peak arrival of the excitation wave beneath the electrode in direct leads from the myocardium,[17] and is believed to approximate the same phenomenon in semidirect leads.[5, 31] Deflection of the retrograde P sometimes may appear to be opposite in direction to that of the sinus P. For example, an electrode opposite a region of early antegrade activation will tend to register a relatively early intrinsic deflection, a small positive deflection of the P and a large negative deflection (figs. 4 and 5). Since this region may be relatively further away from the A-V node, in retrograde activation a larger positive deflection of P and a later intrinsic deflection will occur.

Fusion P waves are reliable evidence of retrograde conduction. These not only differ distinctly in contour from the sinus P waves (figs. 2*B*, and 5, upper tracings), but may be recognized also as intermediate in character between P waves produced by retrograde activation and those produced by antegrade activation (fig. 3). For the recording of fusion atrial beats, lead II and other remote leads seem to be particularly unsuitable, while an esophageal lead may be most advantageous. Two simultaneous excitation waves traveling

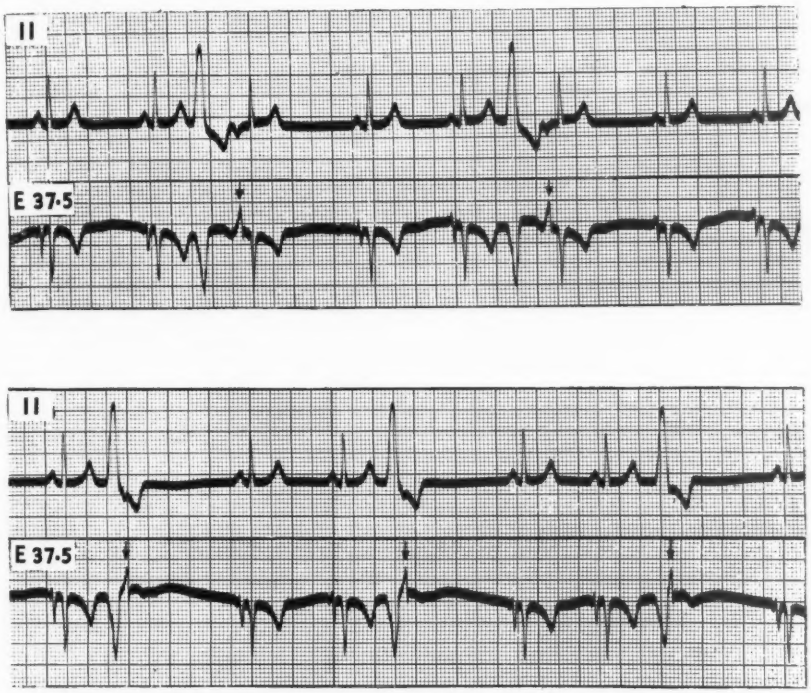

FIG. 4 (Case 4, table 1, as in fig. 3). The arrows point to the retrograde P waves which differ in contour from the sinus P waves. In the lower tracings the retrograde P waves are also premature with respect to the expected sinus P wave. In the upper tracings the first retrograde P is also premature, but the second retrograde P is slightly "late" on the basis of the immediately preceding P-P interval, and this is explained by the sinus arrhythmia. In lead II of the upper tracings retrograde conduction is clearly indicated by the inverted P, but when the retrograde P occurs sufficiently early after the premature ventricular contraction (last premature complex, lower tracings), there is no evidence of retrograde conduction in lead II. There are reciprocal beats in the upper tracings. In this case there were two discontinuous orders of magnitude of ventriculoatrial conduction times, the shorter times being illustrated in the lower tracings, and the longer times in the upper tracings. See text and figure 7.

in approximately opposite directions toward each other, one from the S-A node and one from the A-V node, should tend to neutralize potential differences between two distant points in such leads. This does not hold for the semi-direct esophageal lead. In fact, if the esophageal electrode is so situated that components of both excitation waves are directed towards it, a tendency to summation of potentials would result.

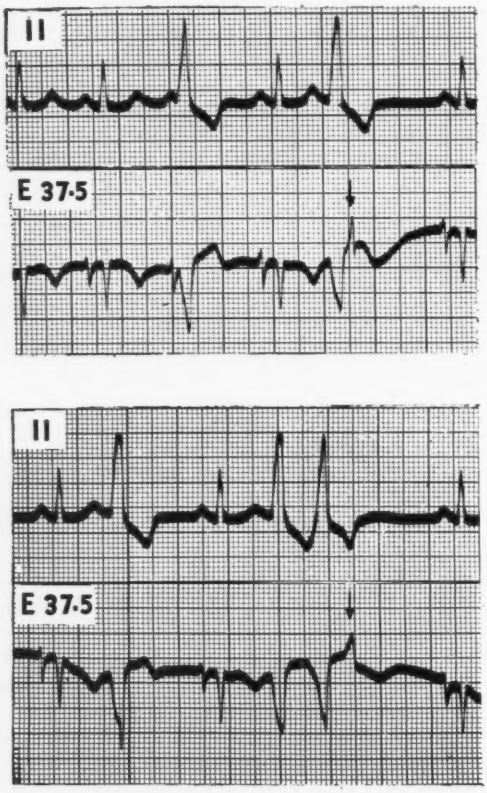

FIG. 5 (Case 6, table 1). Simultaneous records of lead II and an esophageal lead. In the upper tracings the P marked by the arrow is probably due to fusion. In the lower tracings the arrow points to a P produced by retrograde conduction following the second of a pair of premature ventricular contractions. There is no evidence of retrograde conduction in lead II.

Prematurity. The retrograde P waves in figures 1, 2*A*, and 6 occur prematurely with reference to the expected time of occurrence of the regular sinus P wave and interrupt the regularity of the sinus rhythm. Sinus arrhythmia may obscure this relationship (fig. 4). When the retrograde P is premature, the interval to the following sinus P is usually longer than a regular sinus P-P interval (figs. 1, 4 and 6). The evaluation of this interval too may be complicated by sinus arrhythmia.

Retrograde Conduction Time. The interval from the onset of the premature QRS in esophageal leads to the intrinsic deflection of the retrograde P was measurable in all instances except in two, where only fusion P waves were obtained. The interval varied from 0.09 to 0.29 second in all but one of these cases. In this, and in one other case (4 and 8, table 1), which will be discussed separately, there were two discontinuous orders of magnitude of this interval. In the simultaneously recorded E, II and V_1 leads the interval from the earliest onset of premature QRS was 0.11 to 0.29 second. This is close to the range of normal atrioventricular conduction time. The variation of the interval for each case is 0.07 second or less in 9 cases, 0.10 second in one and 0.16 second in another. In cases 4 and 8, the range of variation within each of the two orders of magnitude of retrograde conduction was 0.02 to 0.08 second. These limits support the view that the P wave following the premature QRS is related to the latter and not fortuitous, and the simplest explanation of the relationship is retrograde conduction.

In the standard leads, the hitherto accepted criteria[10, 14, 20] for a P produced by retrograde conduction are its relation to the premature QRS, its prematurity, and its inversion in lead II and sometimes in lead III as well. It is also maintained[10, 20] that the interval from the onset of the premature QRS to the onset of the retrograde P should be longer than the P-R interval of the same case. In only 2, possibly 3, of the 15 cases is retrograde conduction recognizable in lead II. The simultaneous records of esophageal leads and lead II prove that retrograde conduction may be apparent in the former and not discernible in the latter. We believe this explains why the frequency of retrograde conduction in the human has not been recognized previously. Examples are illustrated in figures 3, 4, 5, 6. Figure 4 is of particular

note in this connection. The ventriculoatrial conduction time in this case varied considerably, and only when it was long, was retrograde conduction distinctly recognizable in lead II (upper tracings). When the ventriculoatrial conduction time was sufficiently short, the retrograde conduction was not recognizable in lead II, while still distinct in the esophageal lead (last retrograde P wave, lower tracings). The significant thing about figure 4 is that the lower tracings represent the range of ventriculoatrial conduction time found in 14 of the 15 cases. The ventriculoatrial conduction time in the upper tracings was exceptional in our series and yet it is these tracings that resemble previously reported cases of retrograde conduction.

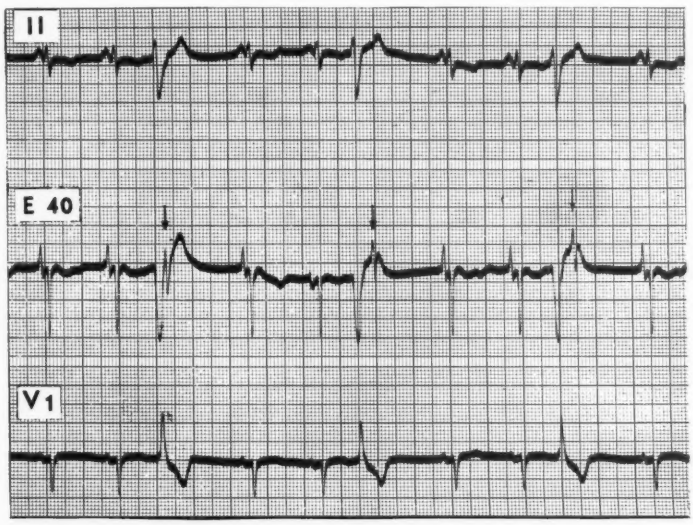

FIG. 6 (Case 8, table 1). Simultaneous record of lead II, V_1 and an esophageal lead. The arrows point to the retrograde P waves which differ in contour from the sinus P waves and are slightly premature with respect to the expected sinus P. There are only poorly-defined deflections in II corresponding to the retrograde P waves of the esophageal leads. There were two discontinuous orders of magnitude of ventriculoatrial conduction time in this case—the short time being illustrated following the first premature complex and the longer conduction time following the second and third premature ventricular contractions. See text and figure 8.

The "Compensatory Pause"

The compensatory pause is often implied to have an absolute value, and the degree of discrepancy within which one may still speak of a compensatory pause is rarely emphasized. In the measurements of this study, however, we sometimes had difficulty in deciding whether or not a compensatory pause was present. In nonphasic sinus arrhythmia, a compensatory pause can be determined only within certain limits. Let us consider, for example, one of the cases of this series with a fairly regular rhythm. The P-P intervals immediately preceding the premature contractions varied within 0.07 second, which means that P-P′-P intervals varying within a range of 0.14 second might be considered to be associated with a compensatory pause. If one arbitrarily allows for an additional variability of only 0.01 second at both the upper and lower limits of the P-P interval for errors of measurement, this makes the range of variability of P-P′-P intervals with a compensatory pause equal to 0.18 second. The allowance of such a wide margin in the calculation of the compensatory pause cannot be avoided, and yet it would seem to allow for a number of fortuitous "compensatory" pauses. In the above instance the permissible range of variability of P-P′-P intervals was 20 per cent

of P-P. If we apply the above analysis, there was a compensatory pause (fig. 1) more often than not (fig. 2*A*) following the premature ventricular contractions with definite retrograde conduction in this series.

spontaneous premature atrial contractions which may occur much earlier in the cardiac cycle. This limited prematurity of the retrograde stimulus (table 1) makes the spontaneous discharge of the sinus node more likely.

TABLE 1.—*Summary of Data in Cases of Retrograde Conduction*

Case No.	Diagnosis	Prematurity of Retrograde P (P-P minus P-P′) Seconds ×100			R′-I′† Seconds ×100	P-R‡ Seconds ×100	"Compensatory Pause"
		A*	B*				
			Min.	Max.			
1	No heart disease	03 to 07	02 to 04	03 to 07	24 to 27	19	some
2	No heart disease	01 to 17	−10 to 14	02 to 20	16 to 18	17	all
3	No heart disease	−01 to 22	−08 to 09	−01 to 22	09 to 19	12	some
4§	No heart disease	−13 to 26	−21 to 23	−14 to 26	16 to 24 42 to 48	12	some
5	?	01 to 23	0 to 21	01 to 29	12 to 15	15	some
6	Hypertension, no evidence heart disease	−02 to 11	−02 to 10	0 to 13	22 to 29	16	all
7	Hypertensive heart disease. Digitalis	0 to 07	−01 to 07	01 to 07	20 to 23	15	all
8§	Coronary heart disease	03 to 17	03 to 14	07 to 18	11 to 14 22 to 24	12	some
9	Coronary heart disease	−03 to 01	−03 to 01	−03 to 01	?	18	all
10	Coronary heart disease	−01 to 01	−02 to 0	−01 to 01	?	13	all
11	Myocardial infarct	05 to 17	03 to 14	07 to 17	17 to 21	14	some
12	Myocardial infarct	0 to 20	02 to 17	04 to 19	13 to 20	18	some
13	Rheumatic heart disease, digitalis	01 to 16	01 to 14	02 to 16	10 to 16	13	all
14	Rheumatic heart disease, digitalis	02 to 07	01 to 26	03 to 28	17 to 26	20	some
15	Ventricular aneurysm, etiology undetermined	−04 to 31	−04 to 23	10 to 39	10 to 26	14	some

* A: Based on the single immediately preceding P-P interval.

B: Based on all available immediately preceding P-P intervals (1 to 10), giving a minimum (Min.) and maximum (Max.) value. Zero and negative values indicate that the retrograde P was recognizable by contour even though not premature.

† From the onset of the premature QRS in the esophageal lead to the onset of the intrinsic deflection (I′) of the retrograde P following it, recorded only when the latter was premature with respect to the expected sinus P wave.

‡ The mean of several P-R intervals.

§ To show the division of R′-I′ into two distinct groups in these two cases measurements from a lead from a single esophageal level were recorded. Measurements in other cases sometimes include leads from more than one esophageal level.

Though the atrium is activated by the retrograde stimulus, it is possible that the sinus node may still discharge spontaneously before the retrograde stimulus reaches it. This undoubtedly accounts for the compensatory pause in a number of the cases. Since the retrograde atrial contraction follows a premature ventricular contraction its degree of prematurity at ordinary heart rates must be limited—unlike

In some instances, the retrograde atrial activation seemed to occur early enough to discharge the sinus node, and yet an apparent compensatory pause occurred. In 4 of the cases with fairly regular sinus rhythm, premature ventricular contractions occurred followed by a compensatory pause when the onset of the intrinsic deflection of the retrograde P was at least 0.14, 0.16, 0.16 and 0.17 second premature

respectively, as measured on the basis of the shortest of the P-P intervals immediately preceding the premature contraction. Since the normal duration of the P wave is less than 0.14 second, such excitation would be expected to discharge the sinus node unless some delay in activation occurs at the latter. The P′-P interval following the retrograde atrial activation is somewhat longer than the P-P interval just as it is following spontaneous premature atrial contractions. It is possible that a slightly decreased P-P′ interval plus a slightly increased P′-P interval should sometimes add up to approximately twice P-P by chance, even though the sinus node is discharged by retrograde atrial activation.

The Ventriculoatrial Conduction Time

As an index of ventriculoatrial conduction time we measured the interval from the onset of the premature QRS to the onset of the intrinsic deflection of the retrograde P (R′-I′ interval). The onset of the retrograde P is frequently impossible to time precisely in the esophageal leads. We use the designation R′-I′ rather than R′-P′ because the latter has been recorded in the literature as a measurement from the onset of the ectopic QRS to the *onset* of the retrograde P. The over-all range of R′-I′ and the variation in a given case have already been discussed and are summarized in table 1. In 10 cases the earliest onset of the premature QRS in the simultaneously recorded esophageal lead and lead II (and often V_1) was measured, and the minimum R′-I′ was equal to or smaller than the P-R immediately preceding it in 5 cases (cases 3, 5, 8, 13, 14, table 1). The interval exceeded the preceding P-R by 0.01 second in one case, 0.05 and 0.07 second in 2 cases each. The minimum R′-I′ is an approach to the ventriculoatrial conduction time least affected by the refractoriness of the conducting tissues. In cases 4 and 8, with two groups of R′-I′ intervals (see below), the minimum R′-I′ was within 0.03 of P-R in the group of shorter intervals, but exceeded P-R by 0.31 and 0.10 second, respectively, in the group of longer intervals. It has been stated that the R′-P′ interval resulting from retrograde conduction is longer than the P-R interval in the same case.[10, 20]

The P-R and R′-P′ intervals are not strictly comparable as an indication of the relative speeds of conduction, since the pathways of antegrade and retrograde conduction are different. Even if it is assumed that the pathways are comparable in length, the two intervals do not necessarily represent relative speeds of conduction under similar conditions, because the conduction from ventricle to atrium occurring early in the cardiac cycle is more apt to encounter refractoriness in the A-V node. For comparison with P-R the same limitations apply, of course, to R′-I′ as to R′-P′.

Winternitz and Langendorf[32] reviewed the literature and tabulated the R-P′ intervals in reported cases of retrograde conduction occurring with incomplete and complete atrioventricular block. Of the twenty-three cases cited by these authors, the R-P′ interval was 0.20 second or less in sixteen. This evidence added to our observations in cases where antegrade conduction was not abnormal does not support the thesis that the retrograde ventriculoatrial conduction time in the human is consistently greater than the normal atrioventricular conduction time.

In experimental animals retrograde conduction to the atria from artificially induced premature ventricular contractions has been observed repeatedly.[4, 7, 18, 21, 23, 27, 29, 30] Some observers found the ventriculoatrial time slower than the atrioventricular time,[4, 27, 29] and others found the reverse.[7, 30] Comprehensive summary and evaluation of the experimental data is difficult. The conditions of the experiments of the different observers are not strictly comparable, and sometimes the experimental conditions during ventriculoatrial conduction differ from those during atrioventricular conduction. Furthermore, there may be differences among animal groups; von Skramlik found atrioventricular conduction faster than ventriculoatrial conduction in frogs,[29] but the reverse in fish.[30]

Comparative data of atrioventricular and ventriculoatrial conduction times in mammals are limited. Both Bayliss and Starling[4] and Stassen[27] found the ventriculoatrial conduction time longer than the atrioventricular time in dogs. The former authors, however, were careful to point out that they made only few observations, and the accuracy of their mechani-

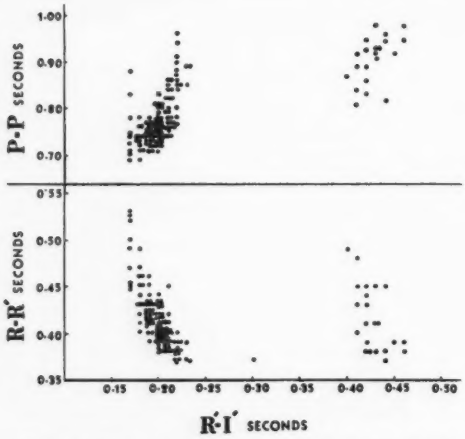

FIG. 7 (Case 4, table 1). Relation of ventriculoatrial conduction time (R′-I′) to cardiac cycle length (P-P) and to time of occurrence of premature ventricular beat (R-R′). Two discontinuous orders of magnitude of R′-I′.

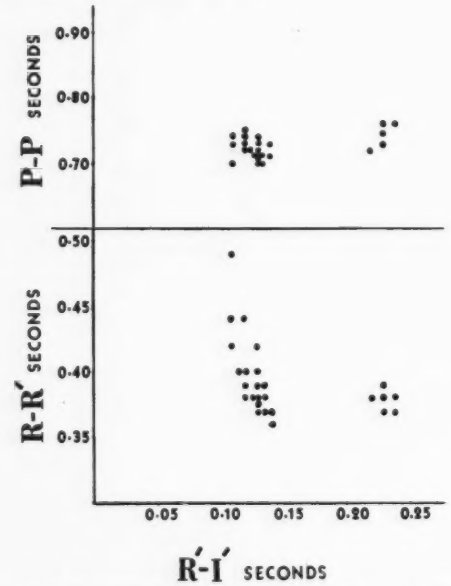

FIG. 8 (Case 8, table 1). Relation of ventriculoatrial conduction time (R′-I′) to cardiac cycle length (P-P) and time of occurrence of premature ventricular beat (R-R′). Two discontinuous orders of magnitude of R′-I′.

cal recording methods were limited, the recording of the onset of atrial or ventricular contraction being questionable. Stassen's measurements were made following ventricular standstill induced by vagal stimulation. Scherf and Shookhoff[23] observed that retrograde conduction occurs readily from induced premature ventricular beats in dogs, and ventriculoatrial intervals as short as 0.08 second were observed. In these experiments A-V nodal rhythm had also been produced, however, so that comparison with the atrioventricular conduction time is not possible. Hukuhara and Komita[12] denied that retrograde conduction occurs in dogs.

In one of our cases (fig. 7) in which numerous premature ventricular contractions occurred at different times in the cardiac cycle, ventriculoatrial conduction time increased the earlier the ectopic ventricular beat occurred. This was interpreted to mean that the earlier a premature contraction occurred the more refractory was the A-V node and the slower the retrograde conduction. In the same case there was considerable sinus arrhythmia and the ventriculoatrial conduction time was proportional to the immediately preceding P-P interval. This is similar to the general relationship that exists between heart rate and atrioventricular conduction time, and suggests a vagal influence on retrograde conduction as well as antegrade conduction. In this same case, however, the P-R variation was only 0.01 second and not discernibly related to cycle length. In one other case in which the measurements could be made, there was a suggestion of the inverse relationship between R-R′ and R′-I′ (group of shorter R′-I′ intervals, fig. 8), but the total range of R′-I′ is rather narrow here compared to the error of measurement. The relationship between heart rate and R′-I′ cannot be evaluated here because of the narrow range of P-P. In the remaining cases there was insufficient variation in heart rate or prematurity or there were too few observations to test these relationships.

Two Cases with Two Orders of Magnitude of Ventriculoatrial Conduction Time

The R′-I′ intervals fall into two discontinuous groups in the two cases (Nos. 4 and 8, table 1), whose electrocardiograms are illustrated in figures 3, 4, and 6 and the data of which are plotted in figures 7 and 8. This dichotomy strongly suggests two pathways of

retrograde conduction, pathways with either absolute differences in rate of conduction or differences in duration of relative refractoriness. So far as we know this has not previously been described.

Retrograde atrial activation did not follow all premature ventricular contractions in the tracings from which figure 7 was charted. Sometimes a regular sinus P wave occurred before retrograde conduction became effective. The intervals the smaller order of magnitude is more apt to occur. A sinus P wave or an R′-I′ interval of the larger order of magnitude follows a premature beat only when the more rapid order of conduction fails, and such failures may be expressed as a proportion of the total number of premature beats in a given range of heart rates. In this case this proportion was found to be distinctly higher at slower heart rates than at fast rates. Exactly what factors asso

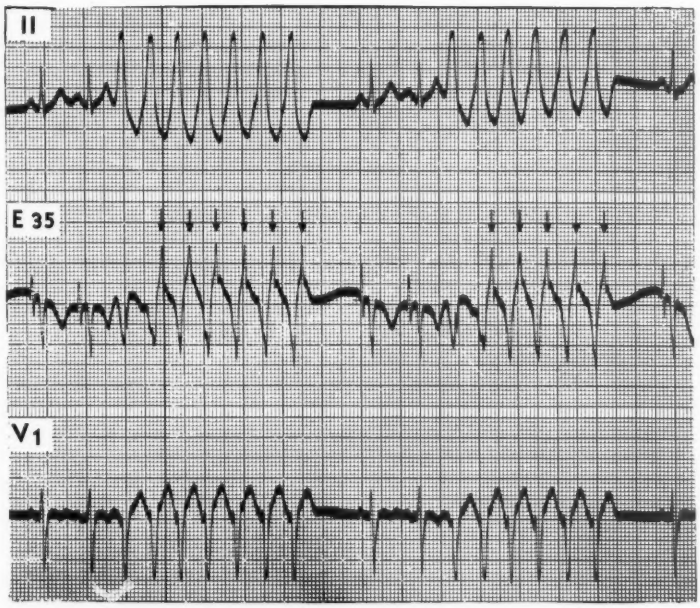

FIG. 9 (Case 3, table 1). Simultaneous records of lead II, V_1 and an esophageal lead. Two short runs of ventricular tachycardia. In the esophageal lead the first QRS of each run has superimposed on it a sinus P and is not followed by a retrograde P whereas each subsequent QRS is followed by a retrograde P. In II and V_1 neither the superimposed sinus P nor the retrograde conduction is recognizable within the ectopic ventricular complexes.

intervals from the premature beats to these regular sinus P waves were consistently intermediate between the two orders of magnitude of R′-I′, and none exceeded the group of long R′-I′ intervals. That is, if the more rapid retrograde conduction failed to occur a regular sinus P might intervene but if the latter did not occur then the slower retrograde conduction never failed.

In figure 7 it is apparent that at the longest P-P intervals the larger order of magnitude of R′-I′ is more apt to occur while at smaller P-P ciated with slower heart rate determine this is not apparent. The R-R′ interval does not seem to influence the order of magnitude of R′-I′ (fig. 7).

Ventricular Tachycardia and Retrograde Conduction

One of the subjects of this study, who had no other evidence of heart disease, manifested frequent brief paroxysms of ventricular tachycardia in addition to frequent isolated premature ventricular contractions. The contour of

the ventricular complexes during tachycardia closely resembled that of the isolated premature beats. In figure 9 are two brief runs of ventricular tachycardia recorded simultaneously in lead II, V_1 and an esophageal lead. In the esophageal lead, superimposed upon the first QRS of each run of tachycardia is the regular sinus P wave, resulting in a W-shaped QRS. That the middle prong of the W is a sinus P wave is apparent from the timing of the previous P-P interval. Each subsequent QRS complex is followed by a retrograde P wave. This retrograde conduction is not apparent in either the simultaneously recorded lead II or V_1.

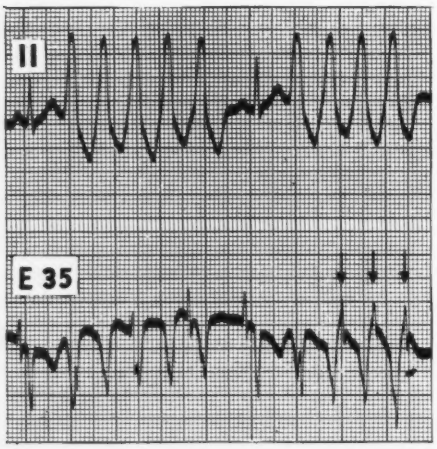

FIG. 10 (Case 3, table 1). Same case as figure 9] Simultaneous record of lead II and an esophagea. lead. Two short runs of ventricular tachycardia. Here *none* of the QRS complexes of the first run is followed by retrograde conduction, and the sinus P waves can be clearly followed in the esophageal lead. Superimposed upon the first QRS of the second run is a sinus P wave in the esophageal lead, and this QRS is not followed by a retrograde P, whereas the three subsequent ectopic QRS complexes are followed by retrograde P waves. In the simultaneously recorded lead II neither the sinus P nor the retrograde conduction are discernible within the ectopic ventricular complexes.

Not all the runs of tachycardia followed this pattern, as illustrated in figure 10 from a record obtained within 15 minutes of figure 9. Here a number of consecutive premature ventricular beats are *not* followed by retrograde conduction. The differences between figures 9 and 10 are possibly due to slight differences in timing of the sinus P wave with respect to the ectopic beats and/or slight differences in refractoriness of the A-V node to retrograde conduction. The different mechanisms shown in the esophageal leads in figures 9 and 10 are not apparent in leads II or V_1.

Retrograde conduction has been considered a possible mechanism of the perpetuation of certain tachycardias after the manner of a circus rhythm. The present study indicates that retrograde conduction is common enough to be considered a possible factor. However, in the case illustrated in figures 9 and 10, the exhibited retrograde atrial activation seems to be an incidental occurrence, since runs of ventricular tachycardia occurred with or without retrograde conduction to the atria. This, of course, does not rule out a circuit through possible A-V nodal or ventricular pathways in this case; it merely excludes the atria as an essential part of the circuit.

The Conditions for Retrograde Conduction

The supposed rarity of retrograde conduction has in the past received two explanations: (1) unidirectional block at the A-V node exists normally, and (2) the relationship between the rate of the human heart and the duration of the refractory period of the atria and node, would only rarely result in atrial response to stimulus from a premature ventricular beat. If our interpretations in this study are correct then the theory of consistent unidirectional block in the human A-V node as a "normal" occurrence is no longer tenable. We would consider the capacity to conduct stimuli in either direction a more "normal" state.

Unidirectional block does occur in A-V dissociation with interference, and while some of these cases occur with digitalis intoxication, rheumatic fever and other abnormal situations, some cases seem to occur in normal hearts. Whatever is the explanation for the unidirectional block in the latter group of cases, its occurrence in exceptional circumstances is not proof of the consistent "normal" existence of unidirectional block in the A-V node. A-V dissociation with interference occurs in "normal"

cases sometimes with pronounced sinus arrhythmia, and possibly intense vagal stimulation is involved in these cases. Experimentally, it is necessary to injure the myocardium in order to produce unidirectional block.[1, 9, 24] Englemann[9] noted a long time ago in frogs that conduction is equally rapid in either direction but that unidirectional block sets in as the animal is dying or as a result of nerve stimulation or toxins. In some cases of incomplete or complete atrioventricular block retrograde conduction to the atria may occur from beats of idioventricular origin.[3, 15, 25, 26, 32] In other words, in these cases there is unidirectional block in the reverse direction, and this is comparable to the unidirectional block produced experimentally as a result of myocardial injury.

The interrelations of the heart rate, the refractory periods, and the time of occurrence in the cardiac cycle of the premature ventricular contraction remain to explain the cases in which retrograde conduction does not occur. In most of the 18 cases in which we did not find retrograde conduction, the reason was quite obvious. In these cases the premature QRS occurred immediately before or after a sinus P so that one might expect the atrium and/or A-V node to be refractory to retrograde activation. In some cases only few of many recorded premature ventricular contractions showed retrograde conduction although long records were obtained, and in some cases records were repeated at different times. In these cases the relationships of the factors under discussion happened to be favorable for these few beats, for example, adequate slowing of the heart rate and sufficient prematurity of the premature ventricular contraction.

Possible Objections to the Interpretations

Two possible objections to our interpretations must be considered: (1) The premature beats we have illustrated may be of nodal origin with aberrant conduction. This cannot be completely ruled out for any so-called ventricular premature beat. However, this series includes only those cases in which the contour of the QRS of the premature contractions differed significantly from that of the regularly occurring QRS complexes. In one case there were premature ventricular contractions from multiple foci with no conventional doubt of their ventricular origin, and contractions from all

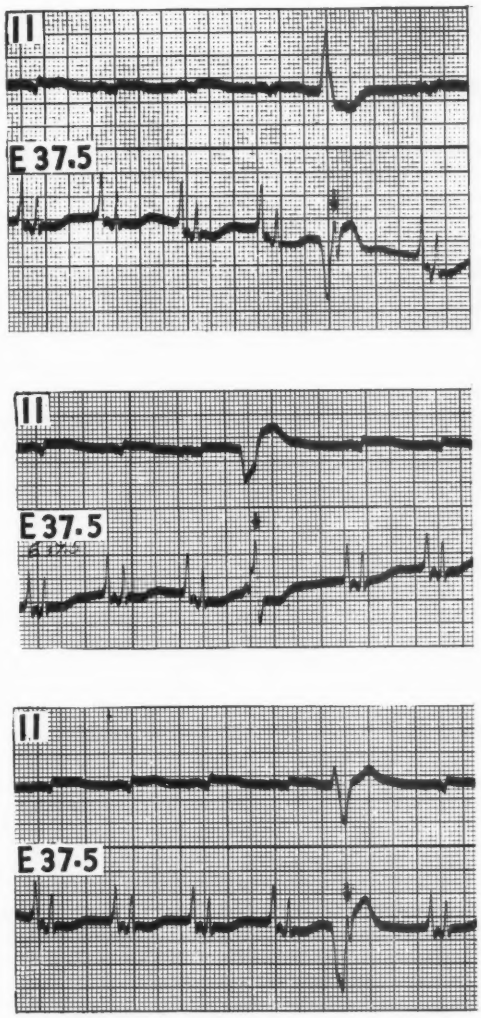

FIG. 11 (Case 13, table 1). Three sections from simultaneous records of lead II and an esophageal lead. Premature ventricular contractions from three different foci, each followed by retrograde P waves (arrows).

foci gave rise to retrograde conduction to the atria (fig. 11).

(2) The P waves following the premature ventricular contractions may be fortuitous pre-

mature atrial contractions not due to retrograde conduction. Against this objection, there were at least several premature ventricular contractions with retrograde conduction in each case in which this interpretation was made. In a number of the cases many premature ventricular contractions with retrograde conduction were studied and in some of the subjects the retrograde conduction was demonstrated repeatedly at different times. In only 2 of the 15 cases, which we believe showed retrograde conduction, did long records show premature atrial contractions that were clearly spontaneous and occurred at times other than immediately following the premature QRS complexes. In one of these there was a single complex of this type, and in the second case there were a number. The P waves which we interpreted as retrograde in these two cases were different in contour from the spontaneous premature atrial contractions occurring at other times. It has already been shown that R′-I′ in the 15 cases as a whole is not far from the range of normal P-R, and R′-I′ in a given case falls within a narrow range. These facts also are against the fortuitous nature of the atrial contractions and favor retrograde conduction.

Summary and Conclusions

1. Retrograde conduction to the atria from premature ventricular contractions was demonstrated in 15 of 33 unselected individuals by means of esophageal leads. The large, peaked P waves obtained in esophageal leads from the atrial level are favorable for this study. In 12 of these 15 cases the esophageal leads were recorded simultaneously with lead II, and in most of these cases the retrograde conduction is not recognizable in lead II.

2. The P wave due to retrograde conduction in the esophageal leads (a) may differ in contour from the sinus P wave, (b) may be premature with respect to the expected sinus P wave in which case the interval to the next sinus P wave is longer than a sinus P-P interval, and (c) occurs within a limited range of time following the premature QRS.

3. A compensatory pause may or may not be present with retrograde conduction. Some of the cases with a compensatory pause may be explained by the spontaneous discharge of the sinus node before the retrograde impulse reaches it. The limited degree of prematurity of the retrograde atrial activation following an antecedent premature ventricular contraction favors spontaneous discharge of the sinus node. In some cases with an apparent compensatory pause, however, the retrograde atrial activation was sufficiently premature so that this explanation does not hold, and in these cases the "compensatory pause" is unexplained or fortuitous. The range of variation which enters into the calculation of the compensatory pause is discussed.

4. There is no evidence that the ventriculoatrial conduction time is consistently longer than the atrioventricular conduction time in human beings. Therefore, the human A-V node "normally" conducts in either direction, and there is no evidence for "normal" unidirectional block. The failure of retrograde conduction to occur in some cases may be explained by the interrelationships of heart rate, refractory periods, and time within the cardiac cycle of occurrence of the premature ventricular contraction.

5. In 2 cases in which adequate measurements were possible, the ventriculoatrial conduction time increased the earlier the premature ventricular contraction occurred. This was interpreted to indicate that the earlier a premature contraction occurred, the more refractory was the A-V node. In one of these cases with pronounced sinus arrhythmia, the ventriculoatrial conduction time was also proportional to the cycle length. This suggests a vagal influence on retrograde as well as antegrade conduction.

6. In 2 cases there were two discontinuous orders of magnitude of ventriculoatrial conduction time, and it is postulated that this was due to two separate pathways for retrograde conduction.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Mr. Raymond Flath and Mr. Henry G. Gillem.

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Postural Electrocardiographic Changes in Healed Myocardial Infarction

By Bernard L. Brofman, M.D., Harold Feil, M.D., Herman K. Hellerstein, M.D., and A. Morgan Jones, M.D.

An electrocardiographic study of 110 patients with old myocardial infarction was made. Change of posture, by causing rotation of the heart on its axes, frequently altered the evidence of infarction. These changes were most evident in posterior infarction. The "labeled" area did the following with respect to the exploring electrode: (1) disappeared, (2) if absent in the supine posture, the evidence appeared in one or more of the other postures, and (3) shifted from one exploring electrode position to another.

SINCE the introduction of unipolar leads, the changes in the human electrocardiogram associated with various postures have been clarified. Significant movement of the heart along its long and anterior-posterior axes has been detected by changes in the unipolar limb and multiple chest leads. Jones and co-workers[1] observed that in normal subjects and in patients with right and left ventricular hypertrophy and right and left bundle branch block the heart becomes electrically more vertical in the left lateral posture, horizontal in the sitting posture, and in about one-half of the cases more horizontal and in one-half more vertical in the right lateral posture. In addition, rotation of the heart along the long axis was manifested by changes of position of the transitional zone in multiple chest leads.

In the present study, the effect of posture on the electrocardiogram has been extended to patients with old myocardial infarcts. The area of infarction was considered to be "labeled" by diagnostic QRS and T changes. It was possible to correlate movement of the labelled area with changes in the electrical axis and in the position of the transitional zone.

In the majority of cases of human myocardial infarction healing takes place between the first and second months.[2-4] After healing, the electrocardiographic manifestations will depend upon the size and location of the resultant electrically dead scar. However, this area may be so situated or so small that there may be no effect recorded by the multiple exploratory leads now in use. Absence of electrocardiographic evidence of myocardial infarction in previously proved cases could be due either to morphologic healing without electrocardiographic residua, or to inappropriate orientation of the exploring electrodes to the electrically altered area.

Our study of the effects of change of body posture upon the electrocardiograms of patients with proved (clinical) infarction, and with or without electrocardiographic residua in the supine posture have confirmed the theoretic possibilities that the effects of a labeled area could be made (1) to disappear, (2) to appear in one or more postures, if absent in the supine, and (3) to shift from one exploratory lead to another.

Methods

One hundred and ten patients with a positive history and unequivocal electrocardiographic evidence of acute myocardial infarction were studied one month to nine years following the acute episode. The cases were selected in order to obtain an approximately equal number of those with anterior and those with posterior myocardial infarction. Electrocardiograms consisting of the standard limb leads, the augmented unipolar leads and the six standard precordial leads, using Wilson's central terminal, were taken with the patient in the following four postures: supine, left lateral, right lateral, and sitting erect. (The points were marked on the chest with indelible ink.) The patient was allowed to remain in each posture long enough before taking the electrocardiograms so as to eliminate or minimize any effect on heart rate and other cardiovascular dynamics due to the shift in posture.[5, 6]

The approximate QRS axis and the T axis in

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the standard leads in each posture were estimated by Dieuaide's method[7] and the extent of rotation of the electrical axis in comparison with the supine was thus determined. The electrical position of the heart was estimated from the augmented extremity leads. The extent of rotation about the long axis of the heart was determined by movement of the transitional zone and of the labeled area in precordial leads. Using circumferential leads, Jones and associates have demonstrated that displacement of the anterior transitional zone was accompanied by an oppositely directed displacement of the posterior transition zone, substantiating the concept of rotation upon the long axis.[1] It is possible that in some of the cases in the present series displacement of the transitional zone may have occurred without rotation on the long axis; however, for the purposes of this study, displacement of the transitional zone or labeled area will infer clockwise or counterclockwise rotation of the long axis. Changes with reference to the transverse axis can only be inferred.

The records were then carefully studied for evidence of significant changes associated with the changes from supine to other postures: The appearance or disappearance of a diagnostic Q and T wave in the extremity leads was considered to be significant. Changes in the precordial leads were considered to be significant when they showed a shift of positive findings from one precordial lead to another or the appearance or disappearance of a positive finding (a broad Q wave or a negative T wave), usually in V_6.

Results

Of the 110 patients studied, 100 had some electrocardiographic evidence of an old myocardial infarct in one or more of the four postures. The remaining 10 patients had electrocardiograms which were within normal limits in all postures, despite the previous diagnostic electrocardiograms and clinical evidence of infarction.

Location of Myocardial Infarction. Of these 100 patients there was electrocardiographic evidence of old infarction in the anterior or anteroseptal region in 41, in the posterior wall in 47, and in both anterior and posterior walls in 12.

Abnormal Left Axis Deviation. Arbitrarily setting the normal range of position of the electrical axis of QRS as 0 to + 90 degrees, it was found that abnormal left axis deviation occurred in the supine posture in 45 cases. There were no cases of abnormal right axis deviation. Of the 45 showing abnormal left axis, 25 were posterior infarcts, 19 anterior, and 1 anterior and posterior.

Changes in the Average Electrical Axis. The average electrical axis of the QRS complexes in the 100 cases was +10 degrees in the supine posture, +21 in the left lateral, +16 in the right lateral and +4.5 degrees in the sitting posture.

Changes in the QRS and T Axes. Table 1 summarizes the direction of the shift of the QRS and T axes from the supine to the other postures.

Table 1.—*Direction of Shift of QRS Axis and T Axis in 100 Cases Associated with Changes of Posture from the Supine*

Posture	Axis	Direction of Axis Shift		
		To Left	To Right	No Change
Left Lateral	QRS	28 cases	64 cases	8 cases
	T	24 cases	27 cases	49 cases
Right Lateral	QRS	36 cases	51 cases	13 cases
	T	24 cases	23 cases	53 cases
Sitting	QRS	55 cases	28 cases	17 cases
	T	26 cases	25 cases	49 cases

The assumption of either the right or left lateral postures tended to make the electrical axis become more vertical, whereas in the sitting posture it tended toward the horizontal. The shift of the T axis was independent of the QRS axis.

Rotation about the Long Axis. The direction of rotation about the long axis of the heart is summarized in table 2. In two-thirds of the cases there was no significant change.* When significant rotation occurred in either the right or left lateral postures it was more frequently counterclockwise, whereas in the sitting posture it was more frequently clockwise. The shift of the transition zone coincided with that of the labeled area. Further correlation shows that when the heart tends to become more vertical, counterclockwise rotation occurs twice as frequently as clockwise rotation; on the other hand, when the heart tends to become more horizontal rotation occurs as frequently clockwise as counterclockwise.

Apparent Shift of Old Infarction. Of the 100 cases studied, 27 showed significant changes in the electrocardiogram with shift in posture.

* A significant change in the precordial leads was one in which the transitional zone and the labeled area moved one precordial position to the right or left.

TABLE 2.—*Direction of Rotation of the Heart on Its Long Axis (As Seen from Below) in 77 Cases of Myocardial Infarction Associated with Changes in Posture from the Supine*

Posture	Direction of Rotation on Long Axis		
	Clockwise	Counter-Clockwise	No Change
Left Lateral	12 cases	19 cases	46 cases
Right Lateral	8 cases	16 cases	53 cases
Sitting	18 cases	9 cases	50 cases

changes were considered to be due to rotation of the heart on its long axis.

Of the total of 27 cases, 11 were anterior infarcts, 13 posterior, and 3 combined anterior and posterior.* In the 8 cases in which evidence of an old infarct disappeared or was less diagnostic this was associated with the electrical axis becoming more vertical in 5 cases, more horizontal in 2, and no change in axis in 1. Six of these cases were old posterior infarcts, 1 anterior, and 1 anterior and posterior. Clock-

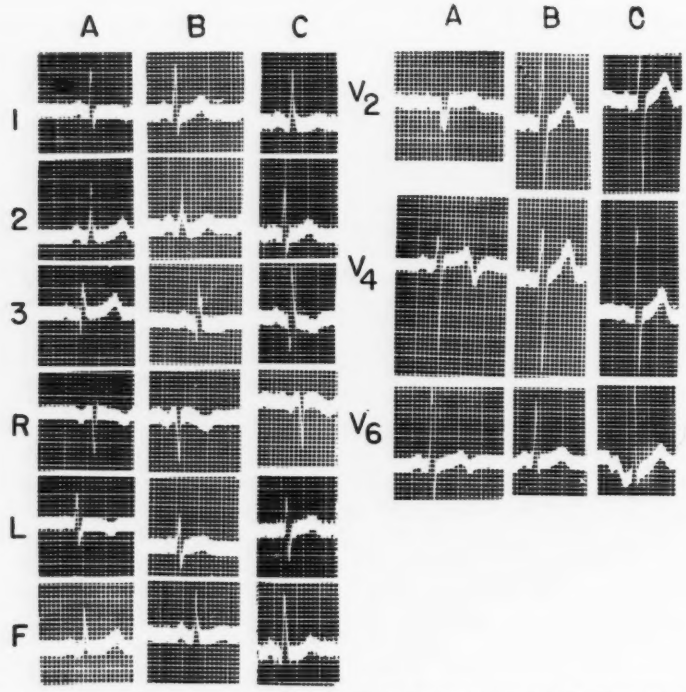

FIG. 1. Serial electrocardiograms showing complete electrocardiographic "healing." Leads 1, 2, and 3, the augmented unipolar leads, and three precordial leads are shown. Under *A* are the diagnostic findings of the acute anterior infarction. The same patient three years later in the supine position is shown in *B*. *C* shows a shift in axis in the sitting position, but still no evidence of the old infarct. In none of the postures could evidence of an old infarct be elicited. Discussion in text.

Considering the supine as the standard posture, in 8 cases it was found that evidence of an old infarct disappeared in the limb leads in one or more of the other postures assumed. Similarly, in 14 cases evidence of an old infarct which was not present in the limb leads appeared in one or more of the other postures. Significant changes in the precordial leads were present in 9 instances, 4 of which had also showed changes in the limb leads. The precordial wise rotation occurred in 3 cases and counter-clockwise rotation in 2. There was no constant relationship between the change in direction of the QRS electrical axis and the direction of rotation on the long axis.

In the 14 cases in which evidence of an old infarct appeared, the electrical axis became

* Approximately the same proportion as the total number studied.

more vertical in 8, more horizontal in 5 and unchanged in 1. Eight of these cases were anterior infarcts, 5 posterior, and 1 combined anterior and posterior. There was clockwise rotation on the long axis in 9 and counterclockwise in 3. Of the 8 cases of anterior infarction in this group significant changes occurred always in association with the electrical axis becoming more vertical, with clockwise rotation in 6 and counterclockwise rotation in 1. Four of the 5 posterior infarcts showed significant changes associated with the electrical axis becoming more horizontal, while in the fifth there was no axis change associated with clockwise rotation on the long axis. (There was correlation between shifts of the electrical axis and direction of rotation on the long axis in that clockwise rotation occurred as the heart became vertical in the anterior infarcts.)

Of the 9 cases which showed significant changes in the precordial leads there were 4 cases in which evidence of an infarct moved medially over the precordium with change in posture, 2 in the left lateral posture, 1 in the right and 1 in the sitting posture. In 2 cases of posterior infarction evidence of lateral involvement appeared in V_6 with counterclockwise rotation. In 1 case of posterior infarction evidence of lateral involvement disappeared with clockwise rotation.

Figure 1 is representative of the 10 cases in which no definite evidence of an old infarct could be seen despite postural change. The diagnostic T-wave changes seen at the time of the acute infarct are no longer present in the supine or other postures.

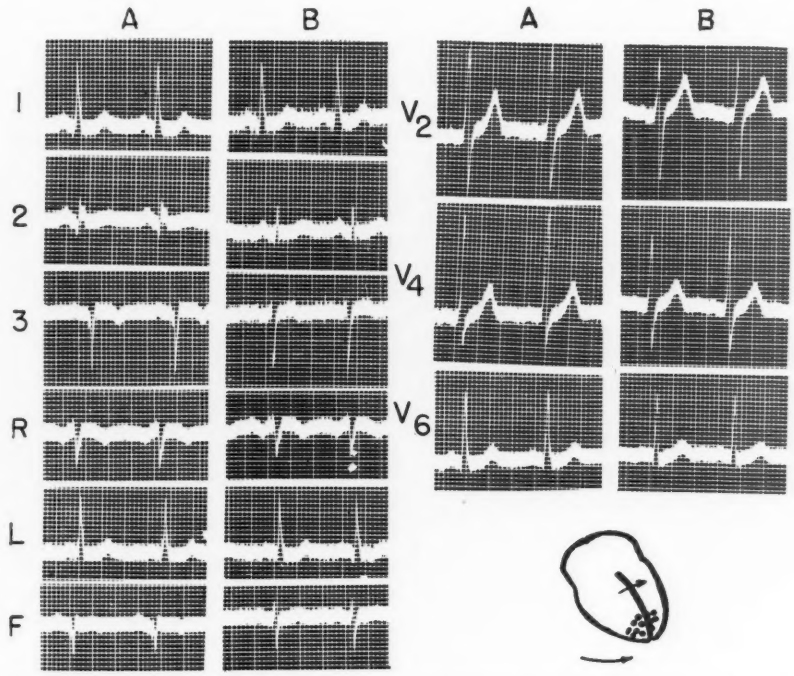

FIG. 2. Positive evidence of an old posterior infarct present in the supine position, *A*; disappears in the sitting position, *B*. Insert shows schematic representation of posterior infarct (stippled); upper arrow represents rotation on long axis, lower arrow QRS axis shift. Discussion in text.

Figures 2, 3, and 4 demonstrate cases in which evidence of an old infarct in the supine position disappeared with change of posture. In figure 2, the deep Q and inverted T present in lead III and in aV_F are absent in the sitting posture. In this case the QRS axis became more horizontal (from −20 degrees in the supine to −30 degrees in the sitting posture), and there was clockwise rotation on the long axis (as viewed from below).

In figure 3, the Q wave present in lead III and in aV_F in the supine is absent in the left and right lateral postures, as the QRS axis shifts from −4 degrees in the supine to 68 degrees in the left and 30 degrees in the right lateral postures. Slight clockwise rotation on the long axis occurs.

In figure 4, the deep Q present in aV_F in the supine disappears in the right lateral posture as the QRS axis becomes more vertical (supine, −16 degrees; right lateral, 0 degrees). There is also clockwise rotation on the long axis so that the terminal T-wave inversion seen in V_6 in the supine moves laterally over the precordium and is not present in the right lateral posture.

Figures 5 and 6 demonstrate cases in which positive evidence of an old infarct not present in the standard supine posture appeared with posture change. In Figure 5 a definite Q wave appears in aV_F in the sitting posture as the QRS axis becomes more horizontal (supine, 5 degrees; sitting, −20 degrees). There is clockwise rotation on the long axis.

In figure 6, a deep Q and more marked inversion of T appear in aV_L in the left lateral posture as the QRS axis becomes more vertical (supine, 45 degrees; left lateral, 78 degrees). There is also clockwise rotation on the long axis so that terminal T wave inversion appears in V_6 in the left lateral posture.

Figure 7 demonstrates a case showing marked changes in the precordial leads associated with clockwise rotation from supine to left lateral posture. The deep QS and T present in V_4 in the supine are present in V_6 in the left lateral. There are insignificant changes in the limb leads.

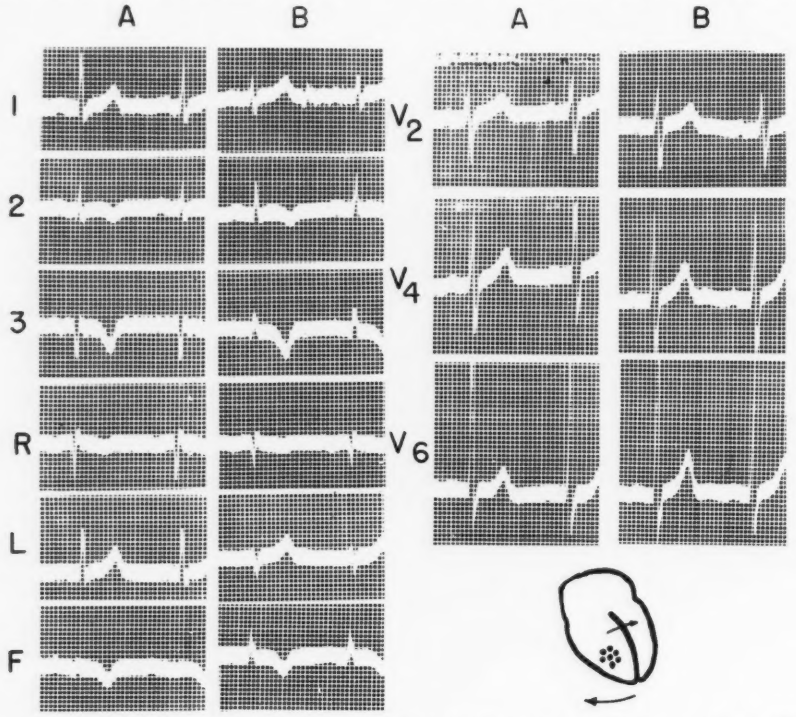

FIG. 3. Positive evidence of an old posterior infarct in the supine (*A*) disappears in the left and right lateral postures (*B*). Insert shows posterior infarct (stippled), upper arrow represents rotation on long axis, lower arrow QRS axis shift. Discussion in text.

DISCUSSION

Variations in the position of the heart are usually referred to in relation to its three axes. (1) Rotation around the anteroposterior axis of the heart results in the long axis becoming more horizontal or vertical. (2) Clockwise rotation on the long axis causes the right ventricle to become more anterior as the left ventricle

becomes posterior, whereas in counterclockwise rotation on the long axis the left ventricle becomes more anterior. (3) With reference to the transverse axis of the heart the apex may rotate forward or backward. Of course any combination of rotation about these axes may occur.

It has been recognized since the earliest days of electrocardiography that the posture of the patient exerts a varying effect upon the positions in the electrical field of the body and changes in the configuration of various complexes result.

In 1909 Grau[12] pointed out that persons with long narrow hearts showed a small R_1 and tall $R_{2,3}$. The effect of rotation of the heart, especially around its long axis, as an important cause of changes in the standard leads has long been established.[13, 14] In 1931 Nathanson studied the effect of change in pos-

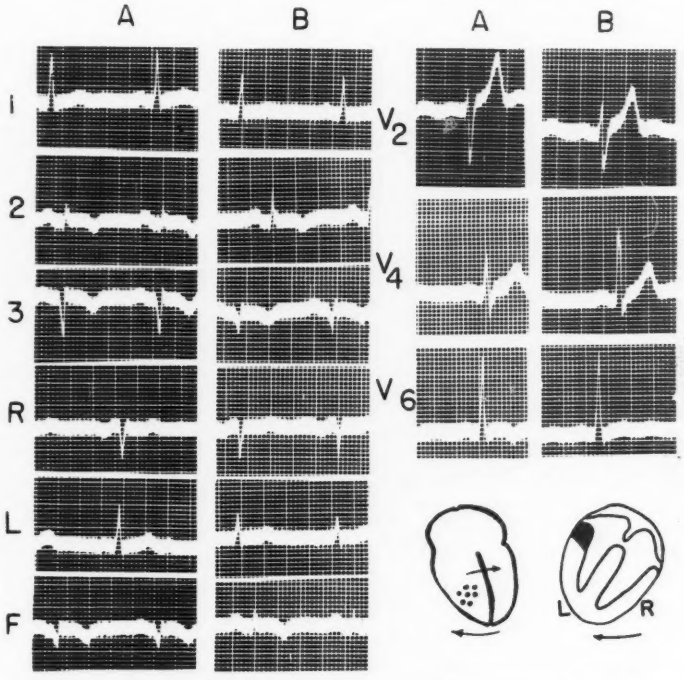

FIG. 4. Positive evidence of an old posterior infarct present in lead 3 and the foot lead in the supine position (*A*) disappears in the right lateral position (*B*). The precordial leads further show clockwise rotation in the right lateral position so that evidence of lateral involvement also disappears. Insert shows posterior infarct (stippled); upper arrow represents rotation on the long axis, lower arrow QRS axis shift. The lateral rotation is also shown in the second insert representing a cross-section of the heart as viewed from above. (R, right ventricle; L, left ventricle).

tion of the heart in the chest and upon the form of the electrocardiogram.[8–10]

Katz and Robinow[11] have shown that changes within the chest account for variations in the electrocardiogram with the shift from the recumbent to the upright posture. The rotation of the heart about its various axes, displacement of the heart as a unit without rotation, and alteration in the contour of the chest cavity are also significant. The summation of these factors produces essential variature in 60 cases from the supine to the left and right lateral. In the left lateral the QRS axis in most cases shifted toward the right although some became more left.[15] In the right lateral there was no change in 30 per cent and the rest went equally to right and to left. Mayerson[16] found a shift of the axis to the right in the upright posture.

Kountz[17] in revived perfused human hearts in normal position found that a shift of the heart to the right caused relative left axis

deviation while rotation to the left caused right axis deviation. Rotation of the heart clockwise caused right axis deviation, while counterclockwise rotation caused left axis deviation.

Numerous continental authors have stressed the importance of the effect of standing on the T waves and have indicated that changes are due to a lack of cardiac reserve.[6, 18] Alterations in coronary blood flow have been postulated by some.[19, 20] Sigler found T-wave alterations in 33 normal subjects when the recumbent and standing postures were compared.[21] He also pointed out changes in the sitting posture. The T-wave changes are presumed to be caused by changes in direction of repolarization.

More recently Master[22] and Gardberg and Ashman[23] have further correlated electrocardiographic patterns and the position of the heart. Jones and Feil[24] found that in left and right bundle branch block lateral postures frequently cause gross rotation of the electrical axis to the right. They stressed the importance of posture change in affecting electrocardiographic patterns, especially in the limb leads.

In our series, on the assumption of the left and right lateral postures, the QRS axis shifted to the right approximately twice as frequently as to the left. Likewise, the average electrical axis for the QRS shifted 11 degrees and 6 degrees to the right in the left and right lateral postures, respectively, while shifting 5.5 degrees to the left in the sitting posture. The degree of shift in the electrical axis was the same in those cases showing significant electrocardiographic differences as in those in which there was no significant change.

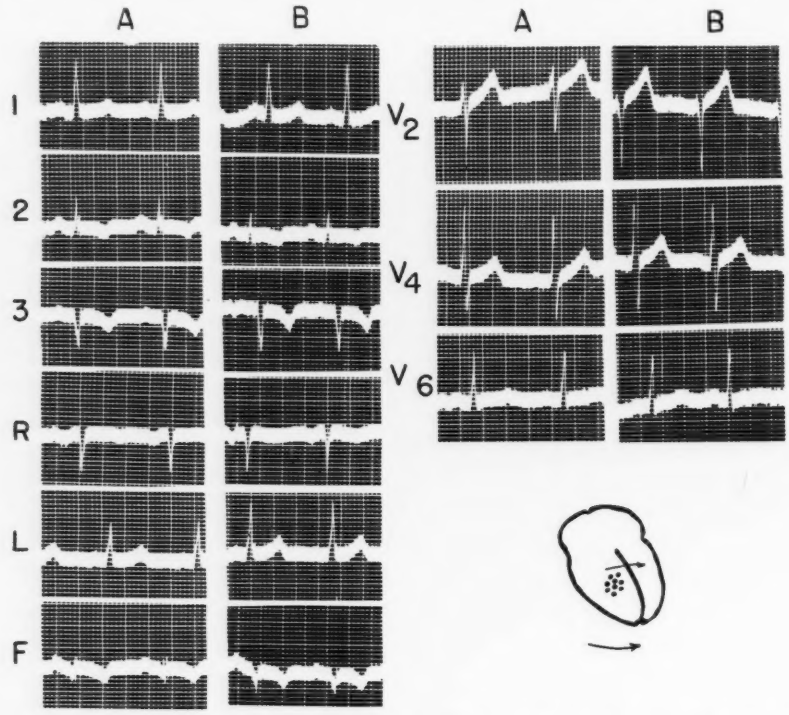

FIG. 5. Equivocal evidence of an old posterior infarct as seen in the foot lead in the supine position (*A*) becomes more diagnostic in the sitting position (*B*). Insert shows posterior infarct (stippled); upper arrow represents rotation on long axis, lower arrow, QRS axis shift.

The average electrical axis for the QRS in the supine posture (10 degrees) showed a marked shift toward the horizontal as compared to the value of 58 degrees[25] usually given for young adults. Goldberger[26] states that electrically the heart lies more horizontal after anterior infarction and more vertical after posterior infarction. However, of the 45 cases showing

abnormal left axis deviation, 25 had posterior infarcts, 19 anterior and 1 anterior and posterior. Mallory and co-workers[2] present data to suggest that infarction per se may lead to cardiac hypertrophy, the average weight of hearts the seat of old myocardial infarction being 503.5 Gm. However, it should be pointed out that the hypertrophy and left axis shift may just as well be a consequence of such accompanying factors as hypertension and valvular disease which tend to cause left ventricular hypertrophy.

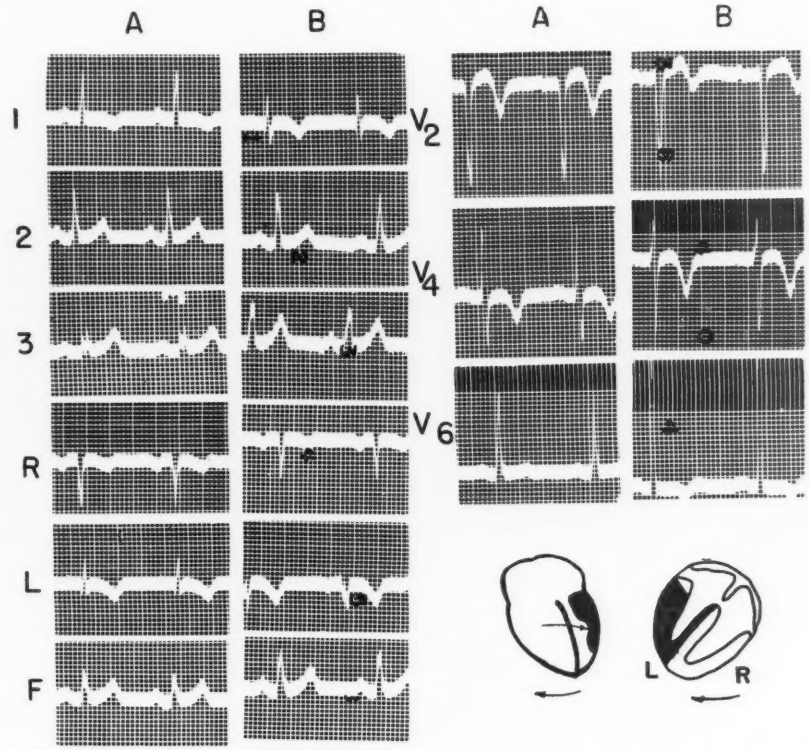

FIG. 6. Positive evidence of an old infarct appears in the left arm lead as posture is changed from supine (*A*) to left lateral (*B*). The precordial leads indicate clockwise rotation so that an inverted T appears in V_6. Insert shows anterior infarct (solid); upper arrow represents rotation on long axis, lower arrow, QRS axis shift. Second insert shows lateral rotation.

According to Levine,[27] during the normal aging process, the left ventricle becomes slightly hypertrophied. Shipley and Hallaran[28] in a study of 200 normal men and women between the age of 20 and 35 found an electrical QRS axis of less than 30 degrees in 10 per cent of the cases. In a study of people over sixty years of age[29] left axis deviation was found in 71 per cent of 300 cases, 61.6 per cent of whom had fluoroscopic evidence of enlargement of the heart. Similarly in a group of 100 people over 70, 62 per cent showed left axis deviation.[30] In 33 cases which subsequently developed left bundle branch block Jones and Feil[31] found an average QRS axis of −6 degrees. With left bundle branch block the axis became −18 degrees.

Presumably the tendency to left axis deviation found in our series is merely a result of the factors which operate in those hearts predisposed to myocardial infarction. Certainly hypertension and myocardial ischemia due to progressive coronary artery disease are prominent factors in these hearts.[32]

The degree of shift in position of the heart in various postures varied greatly in individual cases. Changes in the electrocardiogram depended upon the relative mobility of the heart

and other mediastinal structures and the electrical conductivity of tissues contiguous to the heart in so far as the distribution of cardiac action potentials are affected.[33, 34]

Of the 110 cases studied it was possible to elicit evidence of an old infarct in 100. In the other 10 cases, despite some degree of change in position of the heart with respect to the electrodes brought on by postural change, the scar was so situated or so small so as to produce no electrocardiographic manifestation of an old infarct. Of the remaining 100 cases, positive electrical evidence of an old infarct was present in 73 cases in all postures with no significant change despite varying degrees of rotation about the various axes. In 27 cases there was significant movement of the labeled area associated with rotation of the heart on one or more of its axes. However, the degree of axis shift was not the determining factor in producing significant changes as the degree of shift was equally as great in those cases in which significant changes did not appear.

In 8 cases the scar was so situated that electrocardiographic evidence disappeared in one or more postures as the position of the heart was altered by postural change with a consequent shift of the infarcted area from an electrically effective zone. Similarly in 14 cases there was a shift of the infarcted area; the electrocardiogram showed no evidence of infarction in the standard supine posture while this became evident as the scar moved into the electrical field with posture change. In 9 instances there was significant rotation of the heart on its long axis, clockwise or counterclockwise, so that positive findings shifted in the chest leads. Especially in lead V_6 evidence of lateral involvement appeared or disappeared.

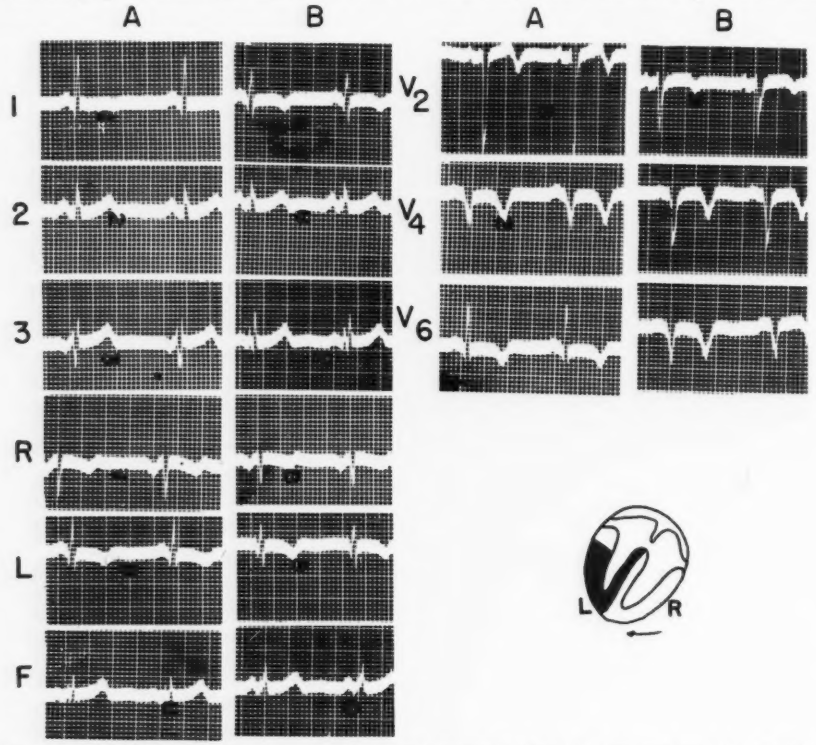

FIG. 7. Marked clockwise rotation on the long axis occurs in the shift from supine (*A*) to left lateral (*B*). Insert shows lateral rotation of anterior infarct.

CLINICAL IMPLICATIONS

In a significant number of cases of old infarction, change in posture can alter the electrocardiogram so that there may be more or less evidence of the old infarct.

The necessity for correlating the precordial

and limb leads is emphasized. In no case did all the evidence of an anterior infarct disappear with respect to all twelve leads. Diagnostic signs of an old anterior wall infarct were present in one or more of the twelve leads in the various postures although diagnostic changes may have disappeared from one or more but not all of the leads. Thus, the diagnosis could still be made in all postures where twelve leads were used.

On the other hand, in the posterior infarcts diagnostic signs did disappear in one or more postures so that the diagnosis could not be made in every position despite the use of twelve leads. This presumably indicates that the electrocardiographic survey of anterior wall lesions with six precordial leads and unipolar limb leads is adequate for the diagnosis of anterior wall lesions. In contradistinction this type of survey is probably not adequate for the diagnosis of posterior infarcts in any or all postures. The recent work of Myers[35] with posterior chest leads may correct this deficiency.

The Ventricular Gradient

In an attempt to correlate these changes with the ventricular gradient, [36, 37] the gradients were calculated for the cases illustrated in figures 2, 3, 4, 6, 7, using 4 microvolt seconds as a unit.[38] In order to obtain greater accuracy in determination of the gradient, the complexes were projected and photographed at exactly 100 times magnification. The values obtained are given in table 3. Figure 8 indicates the magnitude and direction of change of the ventricular gradients before and after posture change which resulted in significant alteration in appearance of the electrocardiogram.

The cases shown in figures 2, 3, and 4 showed significant alteration in the contour of the electrocardiogram with disappearance of diagnostic evidence of old posterior infarction, associated with posture change. In the case in figure 2, the ventricular gradient occupied an abnormal position in the first sextant as expected in posterior wall infarction.[39] In the sitting posture this shifted toward a more normal position in the sixth sextant with clockwise rotation; at the same time the diagnostic Q wave in the foot lead disappeared. Thus, the gradient reflected the changes which took place in the electrocardiogram.

In the case shown in figure 3, the gradient remained in its abnormal position in the sixth sextant although the angle between G and A_{QRS} and the diagnostic electrocardiographic changes became less marked in the lateral postures. Thus, when the heart became electrically vertical the aV_F reflected nontransmural involvement with delayed repolarization of the posterior wall. In the supine posture the foot lead had reflected transmural infarction.

In the case illustrated in figure 4, the ventricular gradient decreased in magnitude while remaining in the same sextant although the heart had rotated electrically in the right lat-

Table 3.—*Changes in Ventricular Gradient in 5 Cases Which Showed Postural Alteration in the Electrocardiogram*

Posture	Fig. 2		Fig. 3		Fig. 4		Fig. 6		Fig. 7	
	Supine	Sitting	Supine	Left Lateral	Supine	Right Lateral	Supine	Left Lateral	Supine	Left Lateral
G										
Magnitude	13.5	15.8	15.5	13.6	12.1	5.6	15.8	20.5	14.8	10.2
Direction	−15	4.5°	−20°	−35°	−15°	−29°	85°	97.5	77°	100°
A_{QRS}										
Magnitude	9.7	10.9	5.0	1.2	7.1	3.7	7	8.9	4.9	4.2
Direction	−16.5°	−13°	1.5°	65°	−6°	2°	46.5°	87°	42°	75°
Angle Between G and A_{QRS} (Positive: G to left of A_{QRS}	1.5°	17.5°	−21.5°	−100°	−9°	−31°	38.5°	10.5°	35°	25°
A_T										
Magnitude	3.8	6.6	11.1	14.0	5.3	3.2	11.0	11.9	9.4	6.5
Direction	−11.5°	36.5°	−76°	−39°	−28°	−66°	109°	108°	93°	113°

1 unit = 4 microvolt seconds.

eral posture. In this case, as in the case shown in figure 3, the diagnostic Q waves had disappeared although the gradient remained distinctly abnormal.

In the case shown in figure 6, the gradient lay in the fifth sextant as a result of the old anterior infarct. The angle between G and A_{QRS} is abnormal. With electrical rotation, the angle between G and A_{QRS} was reduced but the gradient shifted farther toward the third sextant. The electrocardiographic changes became more diagnostic of old infarction.

In the case shown in figure 7, the ventricular gradient changed only slightly in the left lateral posture, although the electrocardiogram be-

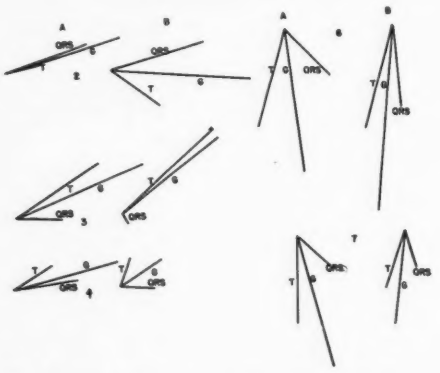

FIG. 8. Graphic representation of ventricular gradient in cases summarized in table 3. *A*, supine; *B*, after posture change.

came more positive with marked clockwise rotation.

In general it may be said that rotation of the area of infarction altered the projection of the vector forces upon the frontal plane and modified the gradient. However, Katz's contention[40] appears to apply, namely, that the ventricular gradient derived from summated vectors may change only slightly while there is great change in the form of the QRS complexes.

SUMMARY

This work was undertaken in order to determine the effect of posture on the electrocardiograms of patients with healed myocardial infarction. The study confirmed the theoretic possibilities that the effects of the scarred area could be made (1) to disappear (2) if absent in the standard position, to appear in one or more postures (3) to shift from one exploratory lead to another.

In 100 cases showing evidence of an old myocardial infarction, significant changes in the electrocardiogram occurred with change in posture from the supine in 27. In 8 (6 posterior infarcts, 1 anterior, 1 combined) evidence of an old infarct disappeared in one or more of the other postures. In 14 (8 anterior, 5 posterior, 1 combined) evidence of an old infarct appeared in the shift from supine. The precordial leads showed significant movement of an old infarction laterally in 5 cases and medially in 2.

The ventricular gradient in 5 significant cases showed no constant correlation with electrocardiographic changes.

Electrocardiographic evidence of an old myocardial infarction may be greatly altered by postural changes in a significant number of instances. The twelve lead electrocardiogram is probably adequate in the diagnosis of anterior wall lesions. In old posterior infarcts posture change produced evidence of lesions which were otherwise not recognizable.

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Abnormal Cardiac Rhythms Caused by Acetylcholine

By DAVID SCHERF, M.D., AND FORRIS B. CHICK, M.D.

The effect of topical administration of acetylcholine on the auricular and ventricular surface of the dog's heart was studied. The experiments show the appearance of variform arrhythmias, particularly auricular fibrillation. The tendency for the development of these arrhythmias is diminished, but not abolished by atropinization. The experiments confirm previous results of the authors according to which auricular flutter is due to a rapid stimulus formation in a center. They help explain the occasional appearance of extrasystoles and paroxysmal tachycardias during vagus stimulation in experimental and clinical observations.

IN ADDITION to the peripherally stimulating action of acetylcholine on structures with cholinergic nerve supply, which is abolished by atropine and known as the muscarinic effect of acetylcholine, Dale, in 1914, demonstrated another action which was similar to that of nicotine. This "nicotinic effect" consists of an intense stimulation of autonomic ganglions and skeletal muscle fibers via the end plates. In recent years there has been increasing evidence that acetylcholine and related compounds also have a stimulating effect on the heart muscle, in distinction to the muscarinic effect which results in cardiac depression.[7, 8, 12, 13]

Most of these investigations are concerned with a study of acetylcholine on the contractility of cardiac muscle; studies on the influence of acetylcholine on the arrhythmias are rare. In dog experiments, ventricular and auricular extrasystoles were observed after intravenous injection of acetylcholine.[6, 16, 19] When acetylcholine was applied to the isolated mammalian auricle, extra contractions appeared.[12] Auricular fibrillation following intravenous administration of acetylcholine or Mecholyl was also seen in dogs.[6, 9, 16] Auricular fibrillation appeared in man after injection of acetylcholine into the carotid artery.[2]

In studies undertaken to investigate the mechanism of auricular fibrillation we applied acetylcholine topically on the sinus node.[23] These experiments led to observations which demonstrated clearly that acetylcholine has a stimulating effect on the heart, in situ.

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This investigation was supported in part by a research grant from the National Heart Institute, U. S. Public Health Service.

METHOD

Twenty-six dogs were used. They were anesthetized with Nembutal and artificial respiration was instituted by tracheal catheter. The sternum was removed and the pericardium was opened. An electrocardiogram was obtained on lead II. Acetylcholine chloride (Roche) in a 5 per cent solution was applied to the head of the sinus node with the aid of a small square of filter paper according to the method of Langendorff. In some experiments 0.05 cc. of the acetylcholine solution was injected subepicardially in the area of the sinus node. In order to apply the drug to the area of the upper auriculoventricular node (coronary sinus node), the heart was lifted from its pericardial bed and the solution of acetylcholine injected into the coronary sinus node through the wall of the coronary sinus vein. It had been shown before that warming of this area led to the appearance of coronary sinus rhythm.[21] The right vagus was exposed in the neck, and, if necessary, stimulated with the aid of a Cambridge Inductorium. Atropine was injected into the superior vena cava in the amount of 0.1 mg. per Kg. of body weight. This is, according to Lewis, adequate for paralysis of the vagus.

RESULTS

Response of Auricles to Acetylcholine in Non-atropinized Animals. The results were uniform in all experiments. Application of acetylcholine by the filter paper method or by subepicardial injection into the head of the sinus node invariably led to the appearance of auricular fibrillation which lasted from a few minutes to 40 minutes. At first there was a brief cardiac standstill and then, suddenly, auricular flutter

appeared which quickly changed to fibrillation, or fibrillation occurred from the start. This standstill was most pronounced when acetylcholine was given by injection and is partly due to reflex action.[20] Single extrasystoles occasionally appeared.

In order to study the mode of onset of the auricular arrhythmia, undisturbed by the activity of the ventricle, we employed faradic stimulation to the right vagus which inhibited the ventricles. The faradic stimulation was applied during the application of filter paper soaked with acetylcholine.

Figures 1*A* and *B* show at first cardiac inhibition during stimulation of the vagus and application of acetylcholine (the string moved because of the manipulation necessary for the application of the filter paper). Immediately after the application of the filter paper, abnormal stimuli are formed in the auricle. In figure 1*A* they appear at first in groups as rudimentary flutter and are then followed by more prolonged periods of flutter and fibrillation. In figure 1*B* rapid flutter appears immediately with a rate of over 600; this increased to about 1000 and was followed by fibrillation. The rapidity with which fibrillation appeared in these experiments was striking. In some experiments, after the appearance of auricular fibrillation, cooling of the area on which acetylcholine had been applied abolished the arrhythmia. In most experiments however, particularly when fibrillation had persisted for more than 20 seconds it was necessary to cool the whole area of the sinus and A-V node in order to reestablish sinus rhythm.[23] Prolonged attacks of flutter did not occur; fibrillation was the rule.

Injection of acetylcholine into the area of the upper auriculoventricular or the coronary sinus node, was performed in eight experiments. The lifting of the heart caused, as figure 1*C* shows, some changes in the electrocardiogram which are readily understandable. Here also the stimulation of the right vagus nerve led to cardiac inhibition. A few seconds after the injection of acetylcholine, flutter appeared with a rate of approximately 1000. This was followed by fibrillation. The flutter waves, however, in this instance showed the deep inverted and peaked form which one expects in lead II when stimulus formation takes place in the area of the coronary sinus node.[21] The form of the QRS complexes and T waves shows that the heart was back in its normal position when the flutter started and that the change in the form of the P waves is not due to the change in position of the heart.

Response of the Ventricles to Acetylcholine in the Nonatropinized Animal. Focal application of acetylcholine to the ventricles led only to the appearance of short, but regular, runs of ventricular tachycardia with a slightly higher rate than that of the existing sinus rhythm. These lasted a few seconds. The high ventricular rate of the sinus rhythm was certainly, at least in part, responsible for the short duration of the ventricular ectopic rhythm. Ventricular fibrillation occasionally followed any mechanical stimulus such as striking the ventricles with a blunt instrument or penetration with a fine needle. Ventricular fibrillation appeared readily following mechanical stimulation of the ventricles when three or more applications of acetylcholine had been made previously to the sinus node.

Response of the Auricles to Acetylcholine in the Atropinized Animal. After complete atropinization of the dog, in only 1 of 22 experiments were we able to produce auricular fibrillation merely by cautious application of acetylcholine on filter paper to the sinus node area. Temporary tachycardias with a rate of about 270 appeared. This tachycardia ceased after a few minutes. For about 10 minutes after the application of acetylcholine, the auricles were extremely irritable and readily went into fibrillation or flutter from the slightest mechanical stimulus. Merely touching the auricles, even at a distance from the site where acetylcholine had been applied, brought about auricular fibrillation for a few minutes (fig. 2). Therefore, subepicardial injection of acetylcholine, which made mechanical manipulation unavoidable, often initiated auricular fibrillation. When atropine was administered during auricular fibrillation, the latter was invariably converted into flutter and sinus rhythm.

Response of the Ventricles to Acetylcholine in the Atropinized Animal. The inclination of the ventricles to fibrillate upon mechanical stimula-

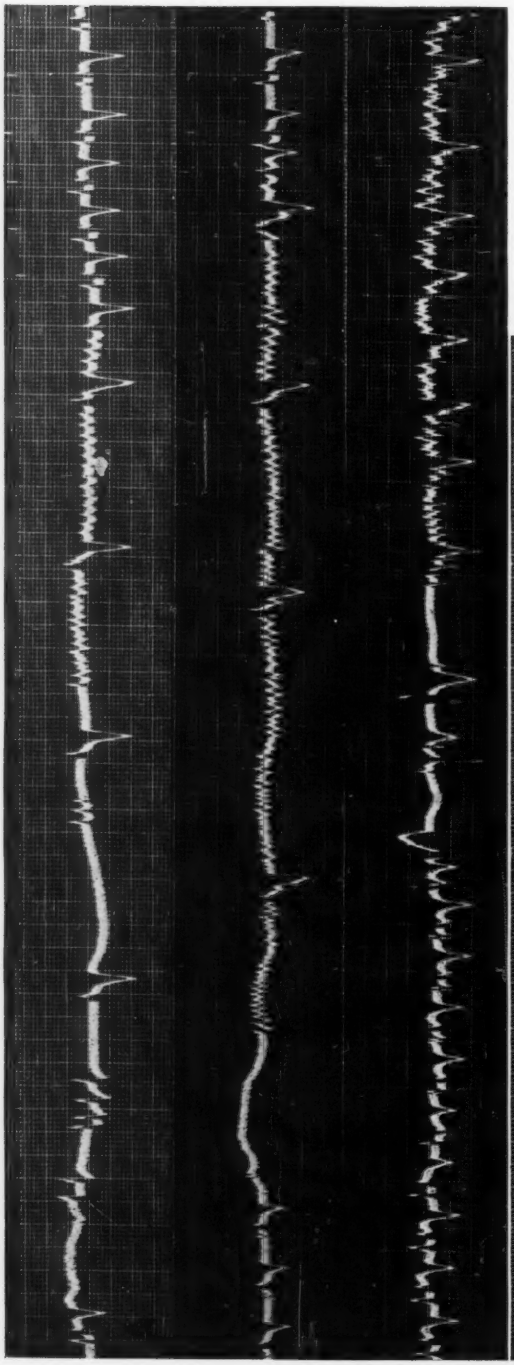

FIGURE 1. Above

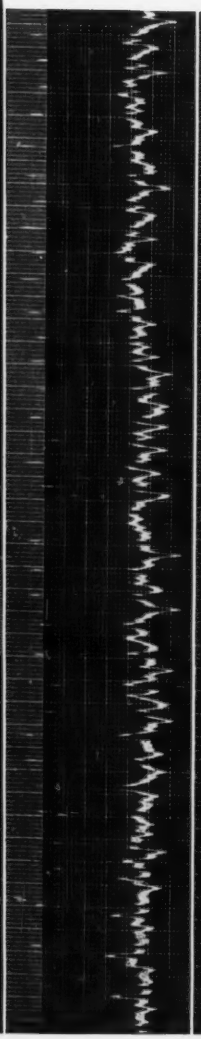

FIGURE 2.

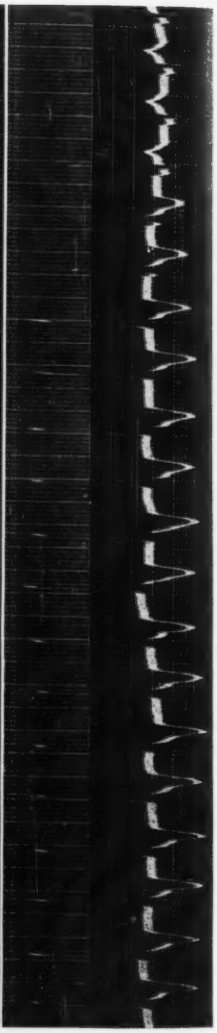

FIGURE 3.

tion disappeared after atropinization. Strong mechanical stimuli, such as striking of the ventricle with a blunt instrument, caused, however, the appearance of ventricular tachycardia. This persisted for 10 to 40 seconds and gradually subsided. It appeared following stimulation at any point of either ventricle. Parasystolic rhythms were often seen.

In the experiment from which figure 3 was taken sinus rhythm was present. Striking the conus area of the right ventricle led to the appearance of ventricular tachycardia with a rate of 130. Figure 3 shows the end of this tachycardia which had lasted 32 seconds.

In five experiments twice as much atropine (0.2 mg. per Kg.) was injected after the intravenous administration of 0.04 Gm. of acetylcholine. Under these conditions mechanical stimuli applied to the auricles or ventricles did not cause abnormal rhythms in three experiments; they were much shorter in two.

Discussion

The experiments described in this paper demonstrate an excitatory effect of acetylcholine on stimulus formation in the heart. The appearance of auricular fibrillation on application of acetyl-β-methylcholine to the dog's auricle in the area of the sinus node has been reported by Nahum and Hoff. These authors, in "some instances," could provoke auricular fibrillation by the application of the drug alone, but it always could be evoked by additional mechanical stimulation of the auricles. We found that the use of larger concentrations of acetylcholine produced auricular fibrillation *regularly* without the addition of other stimuli. While in the experiments of Nahum and Hoff atropine did not affect the arrhythmia once it had been produced, we could always convert auricular fibrillation into sinus rhythm by the intravenous injection of atropine. Finally, in the experiments of Nahum and Hoff, locally applied atropine prevented all effects of acetylcholine. In our experiments the intravenous injection of atropine definitely diminished the tendency to the development of auricular fibrillation, but did not abolish the appearance of auricular fibrillation and of heterotopic auricular and ventricular tachycardias on mechanical stimulation. The differences between our results and those by Nahum and Hoff may be partly due to the fact that acetyl-β-methylcholine has practically no nicotinic action.[29]

Of great interest is the appearance of fibrillation or occasionally flutter following mechanical stimulation. Because of the depolarizing effect of a strong mechanical stimulus leading to the appearance of injury currents, it is understandable that extrasystoles appear for a few minutes after striking the heart with a blunt instrument. In our experiments even the most gentle touching of the auricles after atropinization elicited fibrillation when the heart was under the effect of acetylcholine. Smith and Wilson[28] found that, in the presence of Mecholyl and anoxia, stimulation of the dog's auricle with a feather precipitated auricular fibrillation, while in the absence of anoxia, strong mechanical stimuli were necessary to induce fibrillation. In our experiments, using acetylcholine, slight mechanical stimuli without anoxia had the same effect. Stretch and pressure lead to rapid stimulus formation in skeletal muscle fibers[1] and in the dog's auricle in situ under the influence of aconitine.[25]

The experiments supply support for our contention that auricular flutter and fibrillation are due to rapid stimulus formation and not to a circus movement.[18, 24, 26] It is difficult to believe that the short abortive attacks of flutter shown in figure 1, consisting of only a few beats, are caused by a circus movement, because a circus movement cannot start after a pause

Fig. 1. *A*. Application of acetylcholine to the sinus node during stimulation of the right vagus caused two attacks of rudimentary flutter followed by a short period of fibrillation which changed into flutter and sinus rhythm. *B*. Same procedure as in fig. 1*A*; very rapid flutter appears immediately on application of acetylcholine and fibrillation follows. *C*. Same procedure as in figures 1*A* and *B*; here the auricular flutter which precedes the fibrillation exhibits deeply inverted P waves following application to the A-V node.

Fig. 2. Gentle touching of the auricles results in fibrillation after the administration of acetylcholine.

Fig. 3. End of paroxysm of ventricular tachycardia which had appeared in an atropinized animal after striking the conus area of the right ventricle.

without the presence of a center producing stimuli. At least the first beat of each group must be due to an ectopic stimulus. It may be objected that this ectopic stimulus leads to a circus mechanism, but then the form of the following auricular waves should differ from the first one because the spread of the excitation over the auricles is necessarily different. The slight differences in form of the waves in figure 1 are fully explained by changes in the rate. Furthermore, if auricular flutter were due to a circus movement around the orifice of the great veins independent from the focus of stimulation, as Lewis postulated, the flutter waves, after application of acetylcholine to the auriculoventricular node, should be the same as after application to the sinus node; figure 1*C* shows, however, that the flutter waves always assume the form which one would expect if the stimulus originated at the specific site on which acetylcholine had been applied. One of us has shown earlier[18] that faradization of the auricles leads to auricular flutter exhibiting flutter waves which strikingly resemble the P waves of the prevailing rhythm before faradization.

The experiments demonstrate that after injection of atropine, which prevents any effect of faradization of the vagus nerves on the heart, mechanical stimuli lead to the appearance of auricular fibrillation or ventricular abnormal rhythms, respectively. If larger amounts of atropine were given, mechanical stimulation of the heart was less effective or without results. It is known that large doses of atropine have a direct damaging action on the heart[19] which is probably responsible for this observation.

While there seems to be general agreement that acetylcholine may, under certain circumstances, have a positive inotropic and chronotropic effect, the mechanism of this action still is not clear. Some reports speak in favor of a release of epinephrine-like substances in the heart under the influence of acetylcholine, but certain experimental data obtained by McDowell[12] and Spadolini[30] cannot be fully explained by this mechanism. Our observations do not supply an answer to this problem, but it is interesting to note that local application of epinephrine on the sinus node and ventricle in the concentration of 1:1000 and 1:10,000, following intravenous injection of 0.01 Gm. of acetylcholine in the atropinized dog, did not lead to heterotopic rhythms.

The results of these experiments are of interest to the clinician because they explain certain experiences which are often termed paradoxic. The appearance of ventricular extrasystoles during carotid sinus pressure is so common and so well known that quotation of references does not seem necessary. The appearance of ventricular[14] and auricular[3] tachycardias also has been observed on carotid pressure. Similar tachycardias have been observed in animals during vagal stimulation.[17] Auricular fibrillation was seen to appear on deep breathing[4, 27] or swallowing. These and other paradoxic effects of vagus stimulation on stimulus formation and conduction[19, 24] are more readily understandable when the fact is known that acetylcholine may elicit heterotopic rhythms.

Conclusions

The effect of topical application of acetylcholine to the heart of dogs was studied.

Auricular flutter and fibrillation appeared immediately when a 5 per cent solution of acetylcholine was applied to the sinus node area.

When acetylcholine was injected into the region around the orifice of the coronary sinus vein the flutter waves were negative. This experience and the analysis of the arrhythmias observed at the beginning of the flutter, immediately after application of acetylcholine, are in agreement with the results of previous experiments of the authors according to which flutter and fibrillation were not considered to be the result of a circus movement.

Atropine invariably abolished an existing auricular fibrillation caused by application of acetylcholine.

After atropinization, acetylcholine rarely caused fibrillation; however, the slightest mechanical stimulus applied to the auricles, in form of stretch or pressure, elicited transient fibrillation before and after atropinization which abolished the effect of vagus stimulation. After injection of larger doses of atropine these effects of mechanical stimuli applied to the auricles or ventricles diminished or disappeared.

The ventricles responded in a similar way before and after atropinization but only short periods of tachycardia appeared. Fibrillation

was seen only on mechanical stimulation in the presence of acetylcholine and before atropinization.

Epinephrine applied locally in a concentration of 1:1000 did not cause arrhythmias in the atropinized heart.

The importance of these results for the understanding of the appearance of paroxysmal tachycardias and fibrillation on vagal stimulation in man is discussed.

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CLINICAL PROGRESS

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The Effects of Cortisone and ACTH on the Acute Phase of Rheumatic Fever

By ARLIE R. BARNES, M.D.

MOST of the observations reported in this review will be based on study by my colleagues and me of 14 patients with rheumatic fever, 10 of whom received cortisone and 4 of whom received adrenocorticotropic hormone (ACTH).[1] When observations of others are reported, the source of information will be given.

The results of administering cortisone or ACTH to patients with acute rheumatic fever vary with the severity of the disease but especially according to how early in the course of rheumatic fever these hormones are given. If they are given early in the acute attack, polyarticular symptoms, elevation of temperature and increased heart rates are abolished in one to five days. Prolonged P-R intervals decrease in a week and at two weeks usually are at the normal levels. Sedimentation rates begin to fall rapidly in a week and reach normal levels in from twelve to twenty-one days. In two to three weeks the values for hemoglobin rise sharply and the globulin fraction of the serum protein falls to normal levels. There is a fall in fibrinogen of the blood, which parallels the fall in the sedimentation rate.[2] McEwen and his co-workers[2] noted that the C-reactive protein also fell as the condition of the patient improved. The same observers reported that the antistreptolysin-O titer fell as the condition of the patient improved, but they questioned whether this fact could be attributed to the use of the hormones. When the administration of cortisone or ACTH was discontinued after four or five weeks, some or all of the acute manifestations of the disease reappeared within ten days in a majority of our patients. This phenomenon can best be illustrated by figure 1.

The response to the administration of cortisone or ACTH to patients who have been ill from several to many weeks, particularly if they have carditis, may be much less striking than in the patients treated early in an attack of rheumatic fever. If the hormones are given late in the course of the disease, fever and increased pulse rates may be restored to normal only after many weeks of therapy, and the same is true of prolongation of the P-R interval. Prolonged P-R interval associated with previous myocardial disease may be unaffected in spite of marked clinical improvement of the patient. The sedimentation rate may return slowly to normal, and sometimes it never returns completely to normal. Diminution of heart size occurs slowly if at all and may require four to five weeks for marked changes to occur. And yet in spite of the tardy improvement in these features the patient's well-being, appetite and appearance of toxicity may be altered fairly promptly.

The reappearance of the acute manifestations of the disease after the omission of the hormones occurred with such frequency in our patients that it was concluded that they were capable of suppressing but not curing acute rheumatic fever. We have arrived at the conclusion that rheumatic fever has an inherent duration that varies from individual to individual, and we are doubtful that its duration is shortened by treatment with cortisone or ACTH. Massell and Warren,[3] on the other hand, have expressed the belief that they cured

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the disease in some patients and shortened its course in others.

If our deduction is valid that these hormones do not cure rheumatic fever or shorten its duration, what value do they have in treating the disease? If they have value, then it must reside in their ability to suppress the proliferative reactions in the heart and thus diminish or forestall the subsequent reparative process which results in chronic cardiac disease. Despite the disappearance of murmurs in several of our patients (Massell and Warren[3] co-workers[5] showed that cortisone or ACTH, administered subcutaneously for five days before testicular hyaluronidase was injected into rats intravenously, largely inhibited the increased capillary permeability normally produced by such an injection of hyaluronidase. Dorfman and Moses[6] have demonstrated that ACTH produces a marked decrease of the level of the nonspecific hyaluronidase inhibitor in the serum of patients with rheumatic fever and that this decrease parallels the drop in the sedimentation rate and the patient's clinical improvement. They suggested that this may be a reflection of an effect of the adrenal hormones to change the state of connective tissue so that it no longer reacts to the precipitative stimuli in the disease. An alternate interpretation is considered by these investigators: that the hyaluronidase inhibitor may represent some substance which is released on the destruction of connective tissue. Dougherty and Schneebeli[7] found that adrenal cortical secretions produce anti-inflammatory effects on inflammation produced by an allergen. They concluded that this was an effect on the inflammatory reaction sui generis and was not due to interference with the union of antigen and antibody. These observations suggest at least that these hormones act at the tissue level and that they profoundly

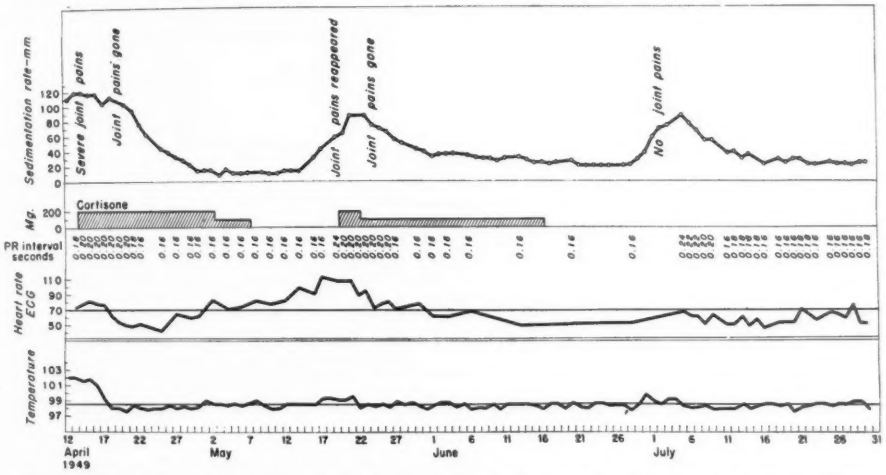

FIG. 1. Effect of administration of cortisone to a boy, 17 years of age, in his first attack of rheumatic fever. Note reappearance of acute manifestations of the disease when administration of cortisone was discontinued.

have reported a similar experience) we must remember that Aschoff bodies may persist for a long time and that murmurs appear in patients several years after apparently full recovery from an attack of rheumatic fever. For that reason these patients will have to be observed for three years or longer before it can be concluded that they have been spared permanent cardiac injury.

We must admit ignorance concerning the mechanism by which cortisone and ACTH act in bringing about improvement in patients with rheumatic fever. In a report by Adams and Dwan[4] it is pointed out that there is an increase in hyaluronidase in rheumatic fever and that this substance has the property of increasing the permeability of membranes. Benditt and

alter cellular reaction and permeability of the cell membrane.

If suppression of the acute manifestations of the disease is a desideratum, it seems important that treatment be started early in the course of the disease and that as complete and continuous suppression as possible be maintained until the acute rheumatic state has reached the end of its natural duration. Figure 2 illustrates our conception of a rational program for the administration of these hormones.

The work of Adams and Dwan[4] is of especial interest with respect to indexes of continued activity of rheumatic fever. They observed that the administration of cortisone and ACTH to patients with acute rheumatic fever caused a fall in hyaluronidase which paralleled the fall in the sedimentation rate. Mucoprotein values did not fall correspondingly. If administration of these hormones was discontinued when the sedimentation rate had returned to normal but while the mucoproteins were still elevated, the acute manifestations of rheumatic fever reappeared. They concluded that a study of the mucoprotein values was a much more accurate index of the persistence of the tissue reactivity in rheumatic fever than was the sedimentation rate. Wilson and Helper[8] regard the count of the circulating eosinophils as probably the most useful guide to therapy with cortical hormone secretion. They consider that treatment is inadequate unless the number of circulating eosinophils drops practically to zero and that a satisfactory therapeutic response consists of a rise during treatment. They found that a fall in circulating eosinophils below the normal range after discontinuation of therapy may indicate the necessity for readministration of ACTH.

The physiologic effects of cortisone and ACTH are many. As Sprague, Power and Mason[9] have pointed out, "some of these effects have favorable therapeutic implications, others are relatively unimportant, while still others may impose hazard upon the patient." These effects may be discussed under the following headings:

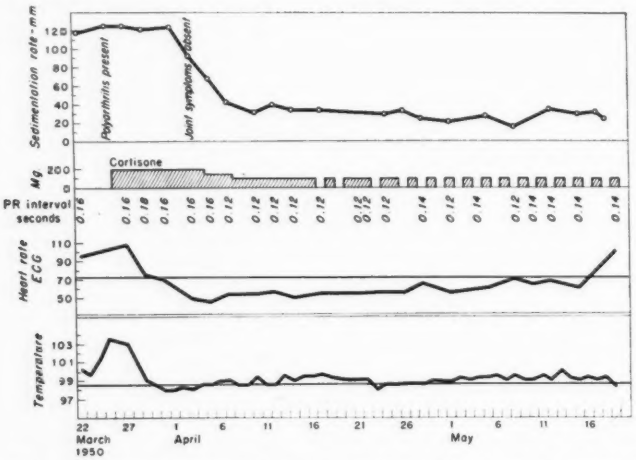

FIG. 2. Adequate, continuous suppression of the acute manifestations of acute rheumatic fever in a woman 24 years of age who received cortisone in her first attack of the disease.

EFFECTS ON CARBOHYDRATE METABOLISM

In the patients of Sprague, Power and Mason[9] doses of cortisone and ACTH were small relative to body weight; and, though slight increases in the level of the fasting blood sugar were sometimes observed, the values have not usually exceeded the normal range. None of our patients with rheumatic fever receiving cortisone or ACTH showed significant elevation of the values of blood sugar.

However, exaggerated diabetogenic effects have been reported by several observers in

patients receiving cortisone and ACTH.[9] This possibility must be borne in mind, and the urine of both diabetic and nondiabetic persons receiving these hormones should be tested for sugar at intervals.

Effects on Protein Metabolism

Large doses of cortisone (200 mg. daily) and of ACTH (105 mg. daily) have been observed to result in a rather decided loss of nitrogen from the body.[9]

Effects on Fat Metabolism

There is some evidence that cortisone and ACTH may mobilize fat stores for conversion into glucose. In several of our patients receiving these hormones pronounced rounding of the facial contour has developed, and there is good evidence that this is a result of deposition of fat in the cheeks.[9] This phenomenon disappeared in a few weeks after administration of these hormones was discontinued.

Effects on Metabolism of Water and Electrolytes

The effect of cortisone and ACTH on the metabolism of water and sodium chloride is variable. In some instances these hormones may cause the retention of salt and water to the point of the production of edema.[9] In none of our patients with acute rheumatic fever did heart failure or an accentuation of previously existing heart failure develop while the patients were receiving these hormones.[1] However, other investigators have observed this to occur while patients were receiving cortisone or ACTH for rheumatic fever.[2, 3] When this occurs, mercurial diuretics must be employed and in some instances administration of the hormone must be discontinued temporarily. These hormones must be administered with unusual caution in patients who have heart failure. In such cases a diet containing not more than 0.5 Gm. of sodium is important in order to avoid the production or accentuation of heart failure.

Hypochloremic, hypopotassemic alkalosis may follow the administration of cortisone in a dose of 200 mg. daily and of ACTH in a dose of 100 mg. daily.[9] The loss of potassium and chlorides from the body may be counteracted by the administration of 2 to 4 Gm. of potassium chloride daily. In none of our patients who received these hormones for acute rheumatic fever did potassium values drop to dangerously low levels.[1]

Androgenic Effects

Mild hirsutism in women was the only androgenic effect observed in our patients receiving cortisone or ACTH.

Effects on Menstrual Function

Menstrual function usually ceased in our patients who received cortisone or ACTH for acute rheumatic fever. These patients all were young, and there is evidence that menstrual function is interrupted much less commonly when these hormones are given to women with long-established menstrual function.[9] In our patients normal menses were resumed within a few months after administration of the hormones was discontinued.[1]

Effects on the Psyche

Along with prompt improvement in appetite and rapid gain in weight many of our patients exhibited marked improvement in feeling and morale. No patient exhibited depression or psychotic behavior. Massell and Warren[3] observed rather severe mental depression in 1 of 20 patients receiving ACTH. We have not observed withdrawal symptoms of asthenia in our patients with rheumatic fever after administration of cortisone or ACTH had been discontinued.

Dosage*

Our experience to date indicates that cortisone should be administered intramuscularly

* Cortisone under the trade name Cortone has been found effective when given orally in the treatment or rheumatoid arthritis. We have not used Cortone orally in the treatment of rheumatic fever, but it would be anticipated that it would be effective. It is suggested that 300 mg. of cortisone be given on the first day and 200 mg. on subsequent days until the acute manifestations of rheumatic fever have been suppressed. The dose can then be reduced to an amount sufficient to maintain suppression of the acute manifestations of the disease. Cortone given by mouth should be given in divided doses (two to four times a day).

in initial doses of 200 mg. daily in the treatment of acute rheumatic fever. This dosage should be maintained for seven to fourteen days or until it is clearly evident that the acute manifestations of rheumatic fever have been largely suppressed. The dose then may be diminished to 100 mg. daily for an additional two to four weeks. This dosage schedule may then be further reduced to 75 mg. daily or 100 mg. on alternate days. When it seems likely that the rheumatic infection is at an end, administration of cortisone may be discontinued. A sharp rise in sedimentation rate coupled with increased duration of the P-R interval, or with manifestations in the joints or both, is probably an indication for resumption of the administration of cortisone. Reappearance of a slight rise in sedimentation and heart rates and a minor rise in temperature may subside without the further use of cortisone.[1, 3] But under those circumstances the patient must be observed closely for evidence of reappearance of gallop rhythm, intensification of murmurs, or prolongation of the P-R interval, in which case the use of cortisone should be resumed promptly. Further study of the count of circulating eosinophils and of levels of mucoproteins in the blood as guides to adequate therapy with cortisone or ACTH deserves very careful investigation.

Initial daily doses of 45 to 60 mg. of ACTH have proved satisfactory in our experience. However, in patients critically ill with acute rheumatic fever, doses of 80 to 100 mg. daily may be desirable for a few days. The program for reducing the dosage paralleling that outlined for cortisone may be followed. Maintenance doses of 25 to 40 mg. daily usually will suffice. The daily dose should be given in divided portions three or four times daily by intramuscular injection.

It does not seem necessary to give much importance to the patient's age and weight in determining the dosage of cortisone or ACTH. A safer guide is the severity of the disease. A patient with severe pancarditis received 2,000 mg. of cortisone in divided doses in the first forty-eight hours of administration, 200 mg. the third day and 100 mg. daily for six days with striking benefit and without untoward effects.[10] While doses of such size are not recommended, this case illustrates the degree to which the drug may be tolerated.

Results

The effect of cortisone or ACTH on rheumatic fever seems to depend on several factors. The most important consideration appears to be the promptness with which the treatment is instituted after the onset of the acute attack of the disease. If the disease has existed for some considerable time (three weeks or more), murmurs may be present which are not abolished by the treatment. On the other hand, in patients treated after a short duration of the disease systolic and diastolic murmurs may develop which disappear during the course of administration of cortisone or ACTH.[1, 3] Similarly, rheumatic carditis treated early in its incipiency responds much more dramatically than it does when treatment is instituted after carditis has existed for many weeks or months.[1–3, 8]

Ten of our patients in their first attack of rheumatic fever and 1 in a recurrent attack received cortisone or ACTH. Six of these patients, when re-examined at periods of 1 to 18 months after their dismissal from the hospital, had no cardiac murmurs or evidence of cardiac enlargement. Two of these patients subsequently have had recurrent attacks of rheumatic fever with reappearance of murmurs and cardiac enlargement.

Five of our patients who received cortisone were considered to have carditis. In 3 patients, in whom the duration of acute rheumatic fever was 15, 16 and 40 days respectively at the time when treatment was started, carditis was improved strikingly after two weeks of treatment. In a fourth patient whose treatment was begun after a recurrence of acute rheumatic fever had existed for 43 days, a marked reduction in heart size and a marked fall in venous pressure were observed after cortisone had been given for one month. In the fifth patient with carditis, in whom treatment was started on the forty-eighth day of the disease, the effect of cortisone on the acute manifestations of rheumatic fever was not pronounced, but there did result a striking improvement in the patient's

appetite, morale and cooperation. Cortisone was administered for one month. A roentgenogram of the thorax made with a portable apparatus six days after administration of cortisone had been discontinued showed a striking reduction in heart size, though the cardiac size still was greater than normal.

McEwen and his co-workers reported a striking benefit in one of their patients with carditis. Massell and Warren considered that ACTH suppressed rheumatic carditis in several of their patients. They considered evidence of this to be the rapid disappearance of signs of pericarditis, regression and disappearance of significant murmurs, and diminished severity of congestive failure. Wilson and Helper treated 11 patients who had carditis with ACTH. Termination of symptoms and disappearance of signs of progressive carditis occurred in every case. They concluded from their experience that the early treatment of acute carditis with adequate amounts of ACTH should shorten the course of the disease, result in minimal residual cardiac damage, and prevent death due to progressive carditis and resultant congestive failure.

This review of our experience and the experience of others of the effects of cortisone and ACTH on acute rheumatic fever leads to the conviction that these hormones are promising weapons in the treatment of the disease. This reviewer believes that the institution of treatment with cortisone or ACTH at the earliest possible time after the onset of the disease is of the utmost importance, and that the course of treatment should be so planned as to maintain suppression of the acute manifestations of rheumatic fever until the disease has reached the end of its natural duration.

Much longer observation of patients treated with these hormones will be required before the ultimate effect of the hormones on rheumatic heart disease can be adequately assessed.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Hunter, T. H.: Speculations on the Mechanism of Cure of Bacterial Endocarditis. J.A.M.A. **144:** 524 (Oct.), 1950.

The author feels that subacute bacterial endocarditis must be treated by direct killing of organisms, and tests for killing, rather than sensitivity tests that measure only inhibition of growth of organisms, must be used to control treatment. He demonstrates that aureomycin and chloramphenicol seem to slow the bactericidal action of penicillin. He explains this action by stating that penicillin has been shown to kill only those organisms which are in the process of active multiplication. If aureomycin or chloramphenicol renders them static, they are no longer killed by the penicillin. He demonstrates that a strain of enterococcus which he used in the tests on aureomycin and chloramphenicol with penicillin was completely killed by using penicillin and streptomycin, whereas neither streptomycin nor penicillin alone would kill the organism. He comes to the conclusion that direct killing of organisms is necessary and that some combinations of drugs seem to be more effective than others. A clinical study is being undertaken to determine whether duration of therapy can be shortened by the use of combinations of drugs which are rapidly bactericidal.

KITCHELL

Lillehei, C. W., Bobb, J. R. R., and Visscher, M. B.: The Occurrence of Endocarditis with Valvular Deformities in Dogs with Arteriovenous Fistulas. Ann. Surg. **132:** 577 (Oct.), 1950.

After observing that animals with large artificially produced arteriovenous fistulas frequently died of endocarditis with severe valvular damage, the authors decided to investigate further a possible causal relationship between the two conditions. The fistulas were made in dogs either in the femoral or the iliac vessels or between the aorta and the inferior vena cava. All were of sufficient size to place a considerable load on the cardiovascular system. After the fistula had been in operation for a minimum of a month, signs of endocarditis were noted in approximately 75 per cent of the animals. Furthermore, in several of them vegetations were also observed at the site of the arteriovenous fistula at the postmortem examination. In all cases with endocarditis, bacteria were found in the blood, although the type of organism varied.

According to the authors, the enormous increase in the work of the heart consequent to the existence of the arteriovenous fistula may have produced traumatic damage to the valves, thus making them vulnerable to any bacteria circulating in the blood stream. The fact that enlargement of the adrenal gland was noted in the dogs with endocarditis suggests that an endocrine factor, due possibly to an imbalance or altered hormone secretion from this gland, may also have played a role.

ABRAMSON

Zimmerman, L. E.: Candida and Aspergillus Endocarditis. With Comments on the Role of Antibiotics in Dissemination of Fungus Disease. Arch. Path. **50:** 591 (Nov.), 1950.

The author reports 3 cases of mycotic endocarditis, in 1 case due to candida (monilia), in the other 2, aspergillus. In 2 cases there was a previous chronic

rheumatic valvulitis. A prolonged febrile course, chronic sepsis, splenomegaly, heart murmurs and embolization were noted in each case. Candida was isolated in blood culture, but at least in 1 case of aspergillus endocarditis blood cultures were repeatedly negative. In reference to this case, the author notes that "contaminants" and "nonpathogens" are not infrequently listed as negatives and that such organisms should be carefully scrutinized before being discarded inasmuch as some of them undoubtedly are mycotic. Another interesting observation is that these 3 patients had received prolonged penicillin therapy, which may have enhanced rather than retarded the development of fungus endocarditis. One patient was a drug addict, a type of individual whose vulnerability to mycotic endocarditis has been previously noted.

The author emphasizes also a structural peculiarity of the mycotic valvular lesions, namely, the large, firm, lobulated and spherical aspect of the vegetations. In his case of candida endocarditis, there was a huge mitral vegetation that measured 2 by 5 cm., involving most of the valvular circumference. Excellent illustrations of the gross and microscopic pathology accompany this article.

GOULEY

Nathanson, M. H. and Liebhold, R. A.: Studies Relative to the Chemotherapy of Bacterial Endocarditis. Ann. Int. Med. **33**: 1224 (Nov.), 1950.

On the basis of in vivo experiments employing specialized laboratory techniques, it is concluded that even in the presence of fibrin, penicillin and streptomycin exhibit antibacterial activity, whereas sodium sulfathiazole and sodium sulfadiazine do not. The inactivity of the sulfonamides is ascribed to their inability to diffuse into fibrin. Since the therapeutic efficiency of a compound in bacterial endocarditis is dependent on its ability to penetrate the fibrin layer of the valvular vegetation, the well established superiority of penicillin and streptomycin over the sulfonamides in the treatment of such infection is understandable.

WENDKOS

CONGENITAL ANOMALIES

Broden, B., Jonsson, G. and Kørnell, J.: Thoracic Aortography in the Diagnosis of Patent Ductus Botalli. Acta radiol. **34**: 65 (July–Aug.), 1950.

The authors describe the method of thoracic aortography as applied to 14 adults and 3 children with patent ductus arteriosus. Opacification of the main pulmonary arteries was the chief diagnostic criterion, but in 6 cases the ductus itself was opacified, and its width and length could be estimated. Localized dilatation of the aorta around the base of the ductus was clearly distinguishable in 7 cases, less definite in 4 others.

SCHWEDEL

Joly, F., Carlotti, T., Sicot, J. R., and Piton, A.: Congenital Cardiopathies. II. The Trilogy of Fallot. Arch. d. mal. du coeur **43**: 687 (Aug.), 1950.

In 1888 Fallot described the combination of pulmonary valvular stenosis, interauricular communication and right ventricular hypertrophy as a special syndrome among the cyanotic group of congenital malformations of the heart. On the basis of 14 observations in which the presence of this triad (trilogy) could be proved, the authors present clinical and laboratory data, which might suggest the diagnosis. The auscultatory findings do not differ from those found in other types of pulmonic stenosis. The characteristic picture is found on x-ray examination, namely, enlargement of the right ventricle, marked (post stenotic) diltation of the main pulmonary artery or its left branch and clear lung fields. The electrocardiogram shows often, but not invariably, the pattern of right heart strain. At catheterization, a high systolic pressure in the right ventricle, exceeding sometimes the systemic pressure, is in contrast to a low or normal pressure in the pulmonary artery and the pulmonary flow is decreased. A right to left interatrial shunt, if present, is usually small at rest, but can be increased by exercising the patient. The disease may be well tolerated up to an age of 30 years, but its prognosis, compared with that of pure pulmonary stenosis, is poor, partly due to a high incidence of subacute bacterial endocarditis. Since the presence of an interventricular communication cannot be proved or excluded in some cases of pulmonic stenosis, the differential diagnosis between the trilogy and the tetralogy of Fallot may become extremely difficult.

PICK

Carlotti, J., Sicot, J. R., and Joly, F.: Congenital Cardiopathies. III. A Study of the Dynamics of Enlarged Pulmonary Arteries. Arch. d. mal. du coeur **43**: 705 (Aug.), 1950.

Twenty two cases exhibiting the roentgenologic sign of a "large pulmonary artery" were divided into two groups. The first group was characterized by marked expansile pulsation of the vessel and included various instances of intracardiac shunt with or without pulmonary stenosis. The second group which showed no pulsation or only transmitted pulsation of the enlarged pulmonary artery consisted of cases of chronic cor pulmonale, mitral stenosis and 2 instances of Eisenmenger's complex. Cardiac catheterization and hemodynamic calculations revealed that the degree of dilatation of the pulmonary artery and the presence of dynamic pulsations could not be correlated with pressure values within the vessel or the amount of pulmonary blood flow.

In the opinion of the authors, dilatation of the pulmonary artery is a protective mechanism to prevent an abnormal rise of pulmonary capillary pressure in the presence of an elevated right ventricular

pressure. In the systemic circulation the pressure difference between aorta and capillaries is effected by a gradual decrease of pressure throughout the length of the aorta and the main arteries. The different mechanism which maintains the pressure gradient in the pulmonary circulation is due to the shortness of the pulmonary vascular tree and its more marked expansibility.

PICK

Lindskog, G. E., Liebow, A., Kausel, H., and Janzen, A.: Pulmonary Arteriovenous Aneurysm. Ann. Surg. **132:** 591 (Oct.), 1950.

The authors report on 4 patients with pulmonary arteriovenous aneurysm, 3 of whom were treated surgically by excision of the involved lobes. In each instance a satisfactory outcome resulted.

With regard to the symptomatology of the condition, bleeding from the nose is a common complaint and hemoptysis may occur to a severe degree. Symptoms of central nervous system origin may be experienced, especially when polycythemia is well developed. These include headache, vertigo, weakness, syncope, convulsions and paresis or paresthesia of the extremities.

The physical findings are principally those of cyanosis in variable degree and clubbing of the digits, but one or both of these may be absent. Frequently multiple "spidery" telangiectasias and discrete nodular hemangiomas of the face, neck, lips and mucous membranes are encountered. Despite cyanosis and dyspnea, the heart is usually found to be normal in size and shape and free of organic murmurs. On auscultation over the site of the aneurysm there may sometimes be heard a continuous rough humming murmur accentuated in systole and in deep inspiration.

Roentgenographic examination is of great importance in making the diagnosis. Generally a saccular, cirsoid or racemose cluster of sharply defined structures with homogenous density is noted, together with enlarged tributary vascular channels. Angiocardiography helps to outline the mass.

ABRAMSON

Brock, R. C., and Campbell, M.: Infundibular Resection or Dilatation for Infundibular Stenosis. Brit. Heart J .**12:** 403, (Oct.), 1950.

The authors report on their first 11 patients with infundibular stenosis as a part of Fallot's tetralogy, who were subjected to infundibular resection or dilatation. Three who died were over 20 years of age; the authors therefore believe that the operation should be avoided in older patients. Seven of the 8 who survived were greatly benefited. A special punch was used to resect the stenotic region. In 2 instances, only dilatation was needed because of the presence of a narrow fibrous ring. Within two months after operation, a slight increase in heart size occurred, which was not progressive. Electrocardiographic changes during the operation consisted of changes in pacemaker and of the appearance of premature beats. A week after operation, cove-shaped S-T segment with T-wave inversion appeared in lead I with reciprocal changes in lead III. The changes progressed for about three weeks and then slowly regressed, disappearing after several months. No clinical changes were associated with these findings.

Infundibular stenosis should be considered in Fallot's tetralogy and in transposition of the great vessels. Angiocardiography can display a large infundibular chamber, best seen in the right anterior oblique position. Demonstration by cardiac catheterization of a sudden drop in pressure within the ventricles just below the valves is also diagnostic. If these findings are not demonstrated, differentiation from pulmonary stenosis can be made at operation when the heart and pulmonary artery are exposed after opening the pericardium.

SOLOFF

CONGESTIVE HEART FAILURE

MacKay, E. M.: Experimental Pulmonary Edema. IV. Pulmonary Edema Accompanying Trauma to the Brain. Proc. Soc. Exper. Biol. & Med. **74:** 695 (Aug.), 1950.

Experimental pulmonary edema was produced in albino rats in a matter of seconds by a blow to the calvaria causing fatal trauma to the brain. This type of pulmonary edema is prevented or reduced in degree by agents which produce a deep narcosis and by adrenergic blocking agents. It has been reported that narcosis prevents experimental pulmonary edema due to epinephrine in some species; narcosis inhibits ammonium pulmonary edema and confers the best protective effect against the lung edema due to massive intracarotid infusions of saline. It is believed that these various types of pulmonary edema are fundamentally similar in origin and that they are all types of neurogenic pulmonary edema resulting from nerve stimuli of central origin. Campbell and Visscher reported that bilateral cervical vagotomy performed immediately beforehand in guinea pigs prevented or reduced the degree of pulmonary edema due to increased intracranial pressure. The author noted the absence of bradycardia, and, at times, the presence of tachycardia. Bilateral cervical vagotomy alone eventually leads to the development of pulmonary edema.

The mechanism in the production of pulmonary edema is complex, and involves other mechanisms than efferent sympathetic stimuli from the brain that may be reduced by narcosis or adrenergic blocking agents and prevented by interrupting the stimuli by sectioning of the vagi.

MINTZ

Vander Veer, J. B., Kuo, P. T., and Marshall, D. S., II: Clinical Experiences with a New Mercurial

Diuretic for Subcutaneous Administration. Ann. Int. Med. **33**: 1215 (Nov.), 1950.

A total of 891 subcutaneous injections of Thiomerin were given to 111 edematous patients. More than 90 per cent of these patients responded satisfactorily. A comparison with Mercuzanthin given intramuscularly showed that the rate of onset, the peak and the duration of the diuresis following administration of equivalent amounts of the two mercurials in the same individual were approximately the same. Symptoms of dehydration and electrolyte imbalance were encountered when the amount of Thiomerin was excessive. A safe and effective dose was found to be 1 cc. subcutaneously at daily or less frequent intervals.

WENDKOS

Hay, S. H., and Wood, J. E., Jr.: Cation Exchange Resins in the Treatment of Congestive Heart Failure. Ann. Int. Med. **33**: 1139 (Nov.), 1950.

Cation resin therapy, by reducing absorption of sodium from the gut, has been most effective in the control of edema due to congestive failure resulting from hepatic cirrhosis, and moderately successful in reducing the distress of ascites resulting from constrictive pericarditis. The resin is more effective than ammonium chloride alone in potentiating the effects of mercurial diuresis. Hypokalemia encountered following the use of the ammonium cation resin does not occur with the ammonium-potassium cation resin. No unfavorable symptoms or signs following the use of the ammonium-potassium cation resin have been observed.

WENDKOS

Sonne, I., and Hilden, T.: Clinical Aspects of Cardiac Asthma and Acute Pulmonary Edema with Special Reference to Blood Pressure. Acta med. Scandinav. **138**: 354, 1950.

A series of 16 cases of cardiac asthma and 42 cases of acute pulmonary edema were studied. Patients in whom these disorders appeared in association with heavy physical exertion or myocardial infarction were excluded.

When the blood pressure recorded during the attack was compared with that observed on the following day it was found to be increased during the attack in all cases of cardiac asthma and in 73 per cent of the cases of acute pulmonary edema. The pressure was decreased in 23 per cent of the patients with acute pulmonary edema. The authors consider the possibility that anoxemia may be the cause of the increase in blood pressure, but point out that the literature indicates that a lowered arterial oxygen saturation is not a constant finding in paroxysmal cardiac dyspnea. They suggest, as a possible explanation, that the elevation in blood pressure is due to some reflexes from the lungs brought about by the increase of the pulmonary congestion during the attack. In those cases in which the blood pressure was decreased, the underlying condition may have been so advanced that a real cardiac failure developed, or unrecognized myocardial infarction may have been present.

The immediate prognosis was distinctly less favorable in those patients with acute pulmonary edema and a diminished blood pressure. Death occurred in 3 out of 4 cases with systolic blood pressure levels lower than 90 mm., whereas there were only 3 deaths in 17 patients with acute pulmonary edema and systolic blood pressures of 190 mm. or more.

ROSENBAUM

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Freedberg, A. S., Blumgart, H. L., Kurland, G. S., and Chamovitz, D. L.: The Treatment of Euthyroid Cardiac Patients with Intractable Angina Pectoris and Congestive Failure with Radioactive Iodine. J. Clin. Endocrinol. **10**: 1270 (Sept.), 1950.

The authors report on 23 euthyroid patients, with intractable and disabling angina pectoris or congestive heart failure, in whom a persistent hypothyroidism was induced with radioactive iodine, I^{131}. The total oral dose of I^{131} given to each patient was from 25.5 to 176 millicuries (average, 61.0). Angina pectoris was abolished or significantly lessened in 11 of 17 patients with intractable cardiac pain. Concomitant congestive failure, present in several patients, was likewise improved. In the remaining 6 of the 17 patients with angina pectoris, the therapeutic result was not striking. In 4 of these patients, although the angina pectoris was definitely lessened when the patients were myxedematous, the latter state caused sufficient discomfort to necessitate the administration of desiccated thyroid, with return of cardiac symptoms. Four of the 6 patients with intractable congestive heart failure showed improvement. The duration of observation varied from three to 22 months and averaged 15½ months. The radiation delivered to the gland sufficient to produce hypothyroidism was calculated as 28,800 to 56,000 equivalent roentgens, compared to an average therapeutic dose of 12,000 in patients with hyperthyroidism. No radiation sickness or toxic effects on the blood or kidneys were observed. Mild or moderate transitory thyroiditis appeared in 18 patients, severe thyroiditis in only one. Temporary mild hyperthyroidism occurred in 2 patients.

CORTELL

Wood, Paul, McGregor, M., Magidson, O., and Whittaker, W.: The Effort Test in Angina Pectoris. Brit. Heart J. **12**: 363 (Oct.), 1950.

A series of 100 cases of unequivocal angina pectoris, selected solely because their electrocardiograms were normal at rest, and 100 normal controls were subjected to an effort test. This test consisted

of climbing up and down a 12 inch step or climbing 84 steps, or less if distress occurred. A ceiling of effort was imposed for practical reasons. Actually, the amount of effort necessary to produce a positive result varied from patient to patient. Ninety-five per cent of those with a heart rate above 90 had positive results, as compared with 5 of 12 with rates below 90. Twenty-six of 30, who had no pain after effort, had diagnostic electrocardiographic changes. The severity of pain was not related to the incidence of positive tests.

The diagnostic changes consisted of a horizontal depression or sagging of the RS-T segment of 1 to 4 mm., a flat T wave, a diaphasic T wave with the initial portion negative, or actual inversion of the T wave. The normal controls, also, commonly developed depressions of the RS-T junction, but the segment sloped rapidly upwards to a normal T peak. Flat depressions not exceeding 0.5 mm. developed in 6 cases.

SOLOFF

ELECTROCARDIOGRAPHY

Ljung, O.: Mild Hypothyroidism Causing Electrocardiographic Changes Suggesting Coronary Insufficiency. Acta med. Scandinav. **137**: 120 (Feb.), 1950.

The author points out that although the electrocardiographic pattern in myxedema is well known, little attention has been paid to the possibility of similar aberrant configurations being present in cases of hypothyroidism in which the typical symptoms of myxedema are absent. There is usually a history of generalized fatigue or of various nervous symptoms in such patients. Shortness of breath is an occasional cardiac symptom. Abnormal electrocardiographic configurations are often seen; abnormal T waves during rest or after exercise or in hypoxemia are the most common change noted. Four cases are presented in which the electrocardiographic findings were chiefly instrumental in establishing the correct diagnosis.

SCHWARTZ

Sjostrand, T.: The Relationship Between the Heart Frequency and the S-T Level of the Electrocardiogram. Acta med. Scandinav. **138**: 201 (July), 1950.

The author studied the relationship of the S-T level of the electrocardiogram to the P-Q level in a group of 70 men and women with normal hearts under the influence of amyl nitrite, methyl scopolamine nitrate, physical work and changes of position. In general, with a rising pulse rate, the S-T level tends to show a slight elevation at first, but later shows an increasingly pronounced depression. The pulse rate at which the S-T level falls below the P-Q level in leads II and CR_6 varied between 70 and 135 per minute and averaged approximately 105 per minute.

The author concluded that physiologic S-T changes can be distinguished from pathologic changes by noting the relation of the S-T depression to the pulse rate. Cases which have at times been regarded as myocarditis or coronary insufficiency in conjunction with fever, nervousness or pain have actually been showing T and S-T depression, which is found in fully normal subjects in connection with a circulatory change.

SCHWARTZ

Sjostrand, T.: Experimental Variations in the T Wave of the Electrocardiogram. Acta med. Scandinav. **138**: 191 (July), 1950.

The author studied the variability of the T wave in 70 persons with normal hearts under various experimental conditions. He found that the T wave diminishes linearly in amplitude with a rise in pulse rate and generally follows the same change under the influence of physical work, methyl scopolamine nitrate, moderate amyl nitrite effect, and sometimes with changes of position. Immediately after physical work, however, or with the head lowered on a tilting table, there is an increase in the amplitude of the T wave despite an increase in the pulse frequency.

At a certain pulse rate the T wave becomes isoelectric and, at higher rates, inverted. The isoelectric pulse rate for T was determined in 52 healthy subjects and was found to vary between 115 and 220 per minute in lead II and between 100 and 220 in lead CR_6.

In general, there are at least two factors which influence the height of the T wave, one generally correlated with the cardiac frequency, and the other related to the position of the body. The author concluded that experimental changes in the circulation may result in pronounced changes in the electrocardiogram of normal individuals, and that electrocardiographic changes may occur secondarily to pathologic circulatory disturbances even though there may be no pathologic change in the myocardium or decrease in its oxygen supply.

SCHWARTZ

Heim de Balsac, R., Cheichi, A., and Vlad, P.: Hiccup and Coronary Disease, with Reference to a Case of Hiccups and Angina Pectoris of Effort. Arch. d. mal. du coeur **43**: 747 (Aug.), 1950.

The authors report the case of a 48 year old man with a history of acquired syphilis and an electrocardiogram indicative of healed posterior myocardial infarction, who on moderate exertion developed regularly an attack of hiccups. It stopped immediately on rest, but was succeeded by typical anginal pain if the patient continued his activity. Both hiccups and pain were relieved promptly by nitroglycerin. In contrast to the not infrequent occurrence of hiccup in the course of acute myocardial infarction, "hiccup of effort" is a rare observation. In view of the prompt action of nitroglycerin, the au-

thors consider coronary spasm as the most probable etiologic factor in the described case.

PICK

Weiss, W.: Electrocardiograms with Prominent S Waves in All Standard Limb Leads, Associated Patterns in Multiple Precordial Leads. Am. Rev. Tuberc. **62**: 307, (Sept.), 1950.

The rare electrocardiographic pattern consisting of predominantly negative QRS complexes due to deep S waves in all standard limb leads was found in 6 of a total 2,850 tracings. Multiple precordial leads were available in 2 cases. In general, this pattern is found in subjects with normal hearts, the position of which is influenced by some extracardiac factor, and in subjects with right ventricular enlargement. In the present series, 4 patients had normal vertical hearts, with right thoracoplasty in 3, and funnel chest in 1 which could have influenced the position of the heart. The other 2 patients had vertical hearts and chronic cor pulmonale. All 6 patients had far advanced pulmonary tuberculosis.

SCHWARTZ

Levy, L., II, Jacobs, H. J., Chastant, H. P., and Strauss, H. B.: Prominent R Wave and Shallow S Wave in Lead V_1 as a Result of Lateral Myocardial Infarction. Am. Heart J. **40**: 447 (Sept.), 1950.

The authors present the electrocardiograms of 12 patients which show a prominent R wave and decrease in amplitude of the S wave in lead V_1. Electrocardiographically, a myocardial infarct was localized in the posterior wall in 3 cases, in the posterolateral wall in 8 cases, and in the anterolateral wall in 1 case. The increase in the amplitude of the R wave and decrease in the amplitude of the S wave are considered to be due to the absence of normal electromotive forces in the opposing ventricular wall.

HELLERSTEIN

Rosenman, R. H., Krause, S., Hwang, W., and Katz, L. N.: The Electrocardiographic Diagnosis of Combined Left and Right Ventricular Strain. Am. Heart J. **40**: 453 (Sept.), 1950.

The authors studied the electrocardiograms of 50 patients with rheumatic heart disease for evidence of combined left and right ventricular strain. Rheumatic heart disease, by virtue of its frequent multiple valvular involvement, often gives rise dynamically to biventricular enlargement. An additional 85 patients with nonrheumatic left ventricular strain were also reviewed. Standard and aV limb and precordial leads (V_1 to V_7, V_{3R} and V_{4R}) were recorded in each instance.

In the rheumatic group, 32 electrocardiograms indicated various types of ventricular strain. The diagnosis of combined ventricular strain (8 cases) was based upon evidence in the precordial leads, some of which pointed to left and some to right ventricular strain. Left ventricular strain was indicated by tall R waves, S-T depression, and/or T wave inversion in the left-sided precordial leads. Right ventricular strain was indicated by tall, usually late R waves, S-T depression, and deep T wave inversion in leads V_{4R} to V_2. In addition, P-mitrale or auricular fibrillation, a vertical "electrical" position and clockwise rotation on the longitudinal axis were commonly present. Combined ventricular enlargement was observed fluoroscopically in this group.

The second group of 85 patients showed the classic pattern of left heart strain in various "electrical" positions. Only one patient presented evidence to suggest concomitant right ventricular strain. Sinus rhythm was present in all but one patient. Moderate to marked clockwise rotation was observed in sixteen electrocardiograms. A vertical or semivertical position and clockwise rotation were affected by emphysema, downward enlargement of the left ventricle in aortic insufficiency, or merely the vertical position usually observed in children.

The authors conclude that the presence of left ventricular strain in a vertical position with clockwise rotation and auricular fibrillation or P-mitrale may be interpreted as evidence of combined ventricular strain in patients with chronic rheumatic heart disease. Similar criteria do not necessarily apply to nonrheumatic patients.

HELLERSTEIN

ENDOCRINE EFFECTS ON CIRCULATION

Moe, R. H., Adams, E. E., Rule, J. H., Moore, M. C., Kearns, J. E., Jr., and Clark, D. E.: An Evaluation of Radioactive Iodine in the Treatment of Hyperthyroidism. J. Clin. Endocrinol. **10**: 1022 (Sept.), 1950.

The authors report the results of treatment with radioactive iodine in 100 selected cases of hyperthyroidism, the basis for selection being (1) recurrent hyperthyroidism, (2) hyperthyroidism with such other pathology as severe heart disease, (3) propylthiouracil failure in patients who did not want surgery, and (4) uncomplicated hyperthyroidism in older individuals. A dose of 100 microcuries per estimated Gm. of tissue was given for diffuse goiter, and slightly more for nodular goiter. The patient was observed at the end of eight weeks, at which time the dose was repeated if no change occurred, or a smaller dose was given if only moderate improvement took place. All the patients responded to radioactive iodine therapy; 88 per cent had a satisfactory remission, 9 became hypothyroid, and 3 became myxedematous. Patients with nodular goiter required on the average a larger number of doses and a greater total dose than did patients with diffuse goiter. Eleven of the 12 patients in whom either hypothyroidism or myxedema developed received only one dose, many of them showing a rapid therapeutic

response. Diffuse goiters decreased markedly in size, whereas nodular goiters became only slightly smaller. No radiation sickness, bone marrow depression or injury to the parathyroids or kidneys were evident.

CORTELL

Simpson, S. A., and Tait, J. F.: Dose Response Studies of the Effect of Desoxycorticosterone Acetate (DOCA) on the Sodium Excretion of Adrenalectomized Rats. Endocrinology **47**: 308 (Oct.), 1950.

The effect of desoxycorticosterone acetate (DCA) on sodium excretion of adrenalectomized rats was studied by determining the rate of excretion of radioactive sodium (Na^{24}) following subcutaneous injection. Injection of DCA led first to a depression of the rate of sodium excretion as compared with that of control adrenalectomized rats, and then to a period of marked increase in the rate of sodium excretion, so that the net total effect was one of sodium loss rather than retention. The duration of the sodium retaining effect of DCA, as well as the degree of retention, was found to be dependent on the dose of DCA for a range of 1.5 to 32 μg. per rat.

CORTELL

Green, D. M., Farah, A., and Klemperer, W. W.: Mechanisms of Desoxycorticosterone Action: Renal Effects of the Water-Soluble Glycoside. Endocrinology **47**: 281 (Oct.), 1950.

A previous report on desoxycorticosterone glycoside (DCG) in human subjects showed that its effect on sodium excretion was the resultant of two contrary actions: a rise in sodium excretion due to an increase in urine volume, and a relative increase in tubular sodium reabsorption. The present study was performed on dogs to determine the effect of the rate of administration of the glycoside, salt-loading and hypophysectomy on these factors. Desoxycorticosterone glycoside consistently caused an increase in water excretion, as a result of a decreased tubular reabsorption of water. It also caused a reduction in urinary sodium concentration, more marked in animals receiving glucose infusions than in ones receiving isotonic sodium chloride, and prevented or reversed by the infusion of hypertonic sodium chloride. One hour after discontinuance of infusions of the glycoside, sodium excretion increased markedly, and water excretion diminished, an effect which could be abolished by hypophysectomy, and possibly due either to increased release of antidiuretic principle from the posterior pituitary, or to the liberation of an antogonist to desoxycorticosterone glycoside from the adrenal cortex through an action on the anterior pituitary.

CORTELL

HYPERTENSION

Murphy, R. J. F.: The Effect of "Rice Diet" on Plasma Volume and Extracellular Fluid Space in Hypertensive Subjects. J. Clin. Investigation **29**: 912 (July), 1950.

The author studied seventeen hypertensive patients on a rice diet with regard to changes in plasma volume, using T 1824, and in extracellular fluid space, using sodium thiocyanate. Over a 14 week period of the rice diet, a decrease of 10 per cent was noted in the plasma volume and 12 per cent in the interstitial fluid volume. These changes were attributed to the low sodium intake, with the loss of body sodium associated with this type of dietary regimen.

ABRAMSON

McNair, J. D., Griffith, G. C., and Elek, S. R.: A Prolonged Study of Oral Veratrum Viride in the Treatment of Essential Hypertension. Am. Heart J. **40**: 382 (Sept.), 1950.

The authors treated 22 patients with essential hypertension with veratrum viride in tablet form for periods varying from two to five months. Each patient was given the maximum dose he could tolerate and was used as his own control by substituting placebos for the drug. Patients who were on a specific diet or were taking sedatives at the beginning of the study were continued on this therapy during veratrum administration. The daily maximum dose varied from 60 to 120 Craw units and averaged 82 units per patient for the group. Analysis of the data showed that veratrum viride in the form used did not produce any significant hypotensive effect in essential hypertension over a prolonged period. These results are at variance with those of Freis who used smaller doses of the drug.

HELLERSTEIN

Davis, L., Tanturi, C. A., and Tarkington, J. A.: Combination of Sympathectomy and Thiocyanates in the Treatment of Experimental and Essential, or Diastolic, Hypertension. Ann. Surg. **132**: 394 (Sept.), 1950.

The authors attempted to investigate the problem of why the combined use of thiocyanates and sympathectomy gave better results in the treatment of hypertension than either approach alone. They injected potassium thiocyanate subcutaneously or intravenously into a series of rats and dogs, and subsequently examined the adrenal glands histologically. Generally, the cortex of the gland showed depletion of lipids in the glomerulosa, inner fasciculi and reticularis layers. Practically the same type of finding was noted in 2 patients who were on thiocyanate therapy and in whom biopsy specimens of the adrenal gland were obtained while a sympathectomy was being performed.

The changes in the distribution of the lipid content in the three layers of the adrenal cortex following thiocyanate administration suggest that this drug has a particular affinity for action upon the adrenal cortex, inhibiting the function of the gland. Since sympathectomy also has such an action, the com-

bination of this operation and thiocyanate therapy produces an additive effect in this regard.

ABRAMSON

Green, D. M., Nelson, J. N., Dodds, G. A., and Smalley, R. E.: Bilateral Adrenalectomy in Malignant Hypertension and Diabetes. J.A.M.A. **144:** 439 (Oct.), 1950.

The authors discuss the relationship of the adrenal cortex to blood pressure and to disturbances of carbohydrate metabolism. They performed unilateral adrenalectomy on 4 hypertensive patients. One died postoperatively of hemorrhage, a second died of hypertensive encephalopathy. The course of the 2 surviving patients has become more benign. One case of bilateral adrenalectomy, a 28 year old woman who suffered from malignant hypertension and diabetes, is reported in detail. A discussion of the improvement in her diabetes and hypertension plus the means of control (by use of aqueous cortical extract, lipoadrenal cortex, and desoxycorticosterone acetate) of her Addison's disease resulting from adrenalectomy is given. The authors do not recommend surgical removal of the adrenal gland as a treatment for either malignant hypertension or diabetes.

KITCHELL

Kappert, A., Sutton, G. C., Reale, A., and Skoglund, K. H.: Studies on the Effect of Hydergin (CCK) upon Hypertension Produced by Noradrenaline. Cardiologia **16:** 129, 1950.

The authors studied changes in blood pressure, pulse rate, skin temperature, and the ear plethysmogram, effected in normal persons by intravenous infusion of noradrenaline (0.007 to 0.02 mg. per minute). They noted an increase of systolic and diastolic pressure due to direct excitation of the adrenergic vasomotor mechanisms. Cutaneous vasoconstriction was not demonstrable in all cases. The systemic hypertension could be abolished by subcutaneous or intravenous injection of 0.3 to 0.4 mg. of Hydergin or prevented by protracted intravenous infusion of the ergot alkaloid. The dose of Hydergin necessary to prevent the pressor effect of noradrenaline is larger than that effective upon adrenaline hypertension. In contrast to essential hypertension, in which a marked cutaneous vasodilation can be seen following Hydergin, this effect is only moderate in hypertension produced by noradrenaline.

PICK

Bayer, O., Blumberger, K. J., and Effert, S.: The Action of Noradrenaline (Arterenol) on Circulation and Heart in Man. Cardiologia **16:** 145, 1950.

The authors applied sphygmographic methods to the analysis of circulatory effects of noradrenaline in normal persons. They noted a first phase of action with increase of the peripheral resistance leading to elevation of systolic, diastolic, and mean pressure, and to a decrease of heart rate and stroke volume. This was followed by a second phase characterized by a simultaneous increase of stroke volume and a fall of peripheral resistance and blood pressure. The time of isometric contraction and ejection increased during the first phase, but were inconstant during the second. Alterations in the circulation can be correlated with and are predominantly due to the reactions of the peripheral vessels. It is probable, however, that nordrenaline also has a direct effect upon the dynamics of the heart.

PICK

PATHOLOGIC PHYSIOLOGY

Brigden, W., Howarth, S., and Sharpey-Schafer, E. P.: Postural Changes in the Peripheral Blood-Flow of Normal Subjects with Observations on Vasovagal Fainting Reactions as a Result of Tilting, the Lordotic Posture, Pregnancy and Spinal Anaesthesia. Clin. Sc. **9:** 79 (May), 1950.

Changes in blood flow in the forearm were studied in various types of subjects tilted from the supine to the erect feet-down position. In normal subjects there was an initial sharp reduction in flow, followed by an increase, but generally the level attained was lower than that observed in the supine position. In subjects in whom cervical sympathectomy had been performed, no change in blood flow was observed with this maneuver. In the upright position a decrease in right auricular pressure and in cardiac output was also noted.

The findings were interpreted by the authors as indicating that when a subject is tilted with the feet down, blood pressure is maintained, despite a reduced venous return, as a result of vasoconstriction of the vessels, not only in the skin and viscera but also in the voluntary muscles of the extremities. If this position is maintained, however, in some subjects vasodilatation will occur in the forearm, associated with a fall of blood pressure, bradycardia and then fainting.

ABRAMSON

Black, D. A. K., Platt, R., and Stanbury, S. W.: Regulation of Sodium Excretion in Normal and Salt-Depleted Subjects. Clin. Sc. **9:** 205 (May), 1950.

Low salt intake was accomplished in 5 normal subjects by placing them on a rice diet, and the amount of sodium in the urine was studied. After five to six days on such a regimen, the effect of infusing hypertonic salt solution was determined. A very low excretion of sodium was observed during the period the subjects were on a salt-poor diet; this was interpreted as a result of increased tubular reabsorption of this ion. The latter reaction persisted after the plasma sodium had been raised to

normal or increased levels by saline infusion. Such a delay in the readjustment to a normal sodium load was explained on the basis of a hormonal mechanism, possibly an overproduction of adrenal cortical hormones during salt depletion.

ABRAMSON

Greenfield, A. D. M., Shepherd, J. T. and Whelan, R. F.: The Average Internal Temperature of Fingers Immersed in Cold Water. Clin. Sc. **9:** 349 (Aug.), 1950.

The authors describe a calorimetric method for determining the average internal temperature of a finger. They believe the method has advantages over that obtainable with thermoelectric junctions. They found that at the height of cold vasodilation due to immersion of the distal phalanx in a stirred calorimeter at 0 to 4°C. the average internal temperature of the finger was 20 to 30 C.

WESSLER

Greenfield, A. D. M., and Shepherd, J. T.: A Quantitative Study of the Response to Cold of the Circulation through the Fingers of Normal Subjects. Clin. Sc. **9:** 323 (Aug.), 1950.

The circulation through the finger during and after local cooling was studied with a finger plethysmograph. Quantitative estimations of heat elimination from the terminal 2.8 cm. of the finger were made with an improved finger calorimeter in order to assign minimal values to blood flow. Immersion of the finger in a water bath between 0 C. and 6 C. caused an initial, almost complete, cessation of blood flow, followed after 5 to 10 minutes by a rapid increase to between 30 and 98 cc. per 100 cc. per minute. Similar but smaller changes in blood flow followed the initial constriction period in fingers immersed between 6 C. and 12 C., whereas at 12 to 15 C. there was no initial constriction and the flows were generally lower than in either of the two preceding temperature ranges.

Pain was felt in the fingers at 0 to 6 C. when the blood flow was sufficiently small; it never occurred during a large cold vasodilatation. Pain was felt when the temperature was low and the temperature gradient between the inside and skin of the finger was small; conversely, pain was not felt when the internal temperature was high and the gradient steep.

WESSLER

Schlegel, J. U., and Moses, J. B.: A Method for Visualization of Kidney Blood Vessels Applied to Studies of the Crush Syndrome. Proc. Soc. Exper. Biol. & Med. **74:** 832 (Aug.), 1950.

Inasmuch as the hypothesis of renal ischemia has gained a growing acceptance as the cause of oliguria and anuria in lower nephron nephrosis, the authors studied the kidney circulation in normal rabbits and rabbits which had been exposed to crush injury, using Trueta's method of producing crush. A fluorescent dye, Thioflavine-S, in a 4 per cent aqueous solution was injected intravenously in the ear vein. This dye has the property of being taken up by the walls of the blood vessels and of making them visible when observed in ultraviolet light.

The results obtained showed that the blood flow in the medulla was decreased as a result of a drop in systemic blood pressure, probably combined with a constriction of the efferent arterioles. The authors were unable to confirm Trueta's results which indicated a by-pass through the juxtamedullary glomeruli.

MINOT

Hwang, H., Rodbard, S., Stamler, J., Gros, G., and Weinberg, S. L.: Studies on Renal Pressor Mechanism and on Vascular Reactivity During Depressor Response to Acute Inflammation in Dogs. Am. J. Physiol. **163:** 430 (Nov.), 1950.

The depressor response to acute inflammation (turpentine abscess) was studied in hypertensive and normotensive dogs. The renal pressor agents renin and angiotonin gave identical responses in both types of preparations in both pre- and post-inflammatory periods. Epinephrine, Pitressin, and tetraethylammonium responses were unchanged by the induction of an acute inflammation. These results indicate that the observed reduction in total peripheral resistance (since cardiac output is unchanged during the sustained hypotension in other experiments on inflammation from this same laboratory) is not due to changes in vascular reactivity of the blood vessels to the vasoactive agents investigated. It is pointed out that since tetraethylammonium did not depress blood pressure to a lesser extent in dogs with abscess than in controls, the hypothesis of a decreased sympathetic tone to explain the reduced total peripheral resistance is not supported by these experiments.

OPPENHEIMER

Kolff, W. J.: Serum Potassium in Uremia. J. Lab. & Clin. Med. **36:** 719 (Nov.), 1950.

This paper deals with serum potassium levels found during the treatment of 16 patients with uremia. In uremia, depending on the stage of the disease and the treatment, the serum potassium level can be low or high.

Nine patients of this group had low serum potassium levels, ranging between 1 and 4 mEq. per liter. Eight of these 9 patients were treated by a forced high-caloric, low-protein diet. In only 3 patients were there paralyses and muscular weakness. The paralyses were not closely correlated with the critical potassium level. The lowest potassium levels and fewest paralyses were seen in those treated with a strict butter and sugar diet. The serum potassium was lowered by the ingestion of carbohydrates, which caused the potassium to be shifted from the

extracellular to the intracellular fluid. Many of the patients needed 2 or 3 or more Gm. of potassium chloride or potassium bicarbonate to maintain a normal serum potassium level. In 2 patients the serum potassium was exceedingly low at one time and high at another time. Seven others had high potassium levels (higher than 9 mEq. per liter). Four patients in this group died, probably from potassium intoxication, and of these patients one had paralysis.

Potassium intoxication is a common cause of death in uremic patients and death usually occurs suddenly. Paralyses, which are clinically indistinguishable from those caused by potassium deficiency, may occur. Death is more often caused by cardiac abnormalities with specific electrocardiographic changes which occur before the paralyses become apparent. The serum potassium was lowered from toxic levels by the Borst diet, the artificial kidney, peritoneal dialysis and by the administration of 1 liter of 40 per cent glucose with 30 units of insulin, given by the cardiac catheter. It is believed that the potassium level is lowered by a shift of the potassium from the extracellular to the intracellular space.

The electrocardiographic changes of hypo- and hyperpotassemia were inconsistent and the author felt that the determination of the serum potassium level was much more reliable.

MINTZ

PHARMACOLOGY

Pugh, L. G. C., and Wyndham, C. L.: The Circulatory Effects of High Spinal Anaesthesia in Hypertensive and Control Subjects. Clin. Sc. **9:** 189, 1950.

In order to study the mechanisms responsible for the marked drop in blood pressure which occurs in hypertensive individuals following spinal anesthesia, the authors measured cardiac output under these circumstances in 9 such patients and in 5 control subjects. They found that the fall in blood pressure in both the hypertensive and in the normal subjects was due primarily to a decrease in cardiac output, for in only one-fourth of the cases was there evidence of a reduction in total peripheral resistance greater than 14 per cent. Although the fall in blood pressure was greater in hypertensive than in normal subjects, the percentage change from resting levels was comparable in both groups.

The mechanism of the fall in cardiac output was considered to be closely related to the reduction in venous filling pressure, this being secondary to relaxation of venous tone as a result of sympathetic paralysis.

ABRAMSON

de Largy, C., Greenfield, A. D. M., McCorry, R. L., and Whelan, R. F.: The Effects of Intravenous Infusion of Mixtures of l-Adrenaline and l-Noradrenaline on the Human Subject. Clin. Sc. **9:** 71 (May), 1950.

The effects of the intravenous administration of noradrenaline and adrenaline were studied in normal human subjects. Adrenaline raised the systolic pressure by about 15 mm. Hg and lowered the diastolic pressure by 5 to 10 mm. Hg. Noradrenaline raised both levels by approximately the same amount. Adrenaline caused a large transient increase in calf blood flow, followed by a smaller secondary rise, while noradrenaline produced a decrease. Both drugs caused a reduction in blood flow through the hand. When the two substances were injected at the same time and in mixtures of equal parts, the adrenaline effects predominated.

ABRAMSON

Strauss, M. B., Rosenthal, J. D., and Nelson, W. P.: The Effect of Alcohol on the Renal Excretion of Water and Electrolyte. J. Clin. Investigation **29:** 1053 (Aug.), 1950.

Evidence is presented that 147 ml. of 86 proof bourbon whiskey (50 gm. of absolute alcohol), administered in the postabsorptive state five hours after breakfast to normal subjects led to increased urinary excretion of water. This was not due to an increase in glomerular filtration rate but rather to a decrease in tubular reabsorption of water. Whiskey diuresis is inhibited by pituitary extract (Pitressin) or salt ingestion. The authors suggest that whiskey diuresis is due to a depression of normal supraopticohypophyseal responsiveness to alterations in tonicity.

WAIFE

Shick, R. M., Baggenstoss, A. H., Fuller, B. F., and Polley, H. F.: Effects of Cortisone and ACTH on Periarteritis Nodosa and Cranial Arteritis. Proc. Staff Meet. Mayo Clin. **25:** 492 (Aug.), 1950.

Cortisone was administered to 4 patients with periarteritis nodosa and to 2 patients with cranial arteritis; 2 others with periarteritis nodosa received ACTH.

All patients experienced prompt and usually dramatic subjective relief after administration of the hormones had been started. Without exception, fever subsided within 24 to 72 hours, whereas sedimentation rates decreased to normal or nearly normal more gradually. Partial clinical relapses occurred in most cases after withdrawal of the hormones, but improvement followed when administration was resumed. Significant improvement of peripheral neuropathy was not observed. The arterial lesions of the fourth patient with periarteritis nodosa who received cortisone showed histologic evidence of healing on completion of the second course of treatment. The patient was still in clinical remission when observed three weeks later.

The two patients with periarteritis nodosa who received ACTH were observed 10 and 11 weeks respectively after treatment. Both had experienced continuous and sustained subjective improvement

and were afebrile. One showed evidence of persistent renal damage and mild hypertension. Biopsy in both cases gave negative results. Except for moderately elevated sedimentation rates, neither presented evidence of reactivation of the primary disease.

The 2 patients who died were observed for 11 weeks and 5 months respectively. One received a total of 3.6 Gm. and the other a total of 13.4 Gm. of cortisone. At necropsy, evidence of complete healing of all arterial lesions was found. However, fibrous obliteration of the lumina of these vessels had occurred, resulting in widespread visceral infarction. In both cases the adrenal cortexes had undergone moderate atrophy and a decrease in lipid content.

Cortisone effected prompt relief of both local and systemic symptoms in the two cases of cranial arteritis. Nevertheless, on follow-up biopsy, characteristics of chronic arteritis were found, and apparently little more healing had taken place than would be expected in the natural course of the disease. Visual complications did not develop in either case and, 10 and 11 weeks respectively after withdrawal of cortisone, both patients were afebrile and asymptomatic.

SIMON

Brunsting, L. A., Slocumb, C. H., and Didcoct, J. W.: Effects of Cortisone on Acute Disseminated Lupus Erythematosus. Proc. Staff Meet. Mayo Clin. **25:** 479 (Aug.), 1950.

Cortisone exerts a salutary influence on the course of acute lupus erythematosus: (1) It suppresses symptoms of arthralgia, fever, eruption, serositis, and brings about improvement in the sense of well-being with euphoria, increased appetite and gain in weight. (2) It increases ability to withstand stress and crises such as are imposed by major operations and infections (ordinarily disastrous in this disease). (3) A degree of remission may occur. These benefits are temporary and depend on the maintenance of adequate dosage; symptoms may return within a few days to several weeks after the hormone is discontinued. Cortisone cannot, therefore, be considered a cure for lupus erythematosus. Relapse occurs when the dose is reduced or the hormone discontinued, and throughout the entire period of administration and afterward, there is little fundamental influence on the characteristic laboratory phenomena and no apparent change in the pathologic reactions of the tissues. There was no interference with the normal processes of healing of wounds, abscesses, ulcers, or the eroded skin lesions of lupus erythematosus while the patients were under the influence of cortisone or ACTH. However, it may be stated that cortisone is an agent, capable of exerting some measure of control over the progressive decline usually associated with acute lupus erythematosus.

SIMON

Greiner, T., Gold, H., Cattell, M., Travell, J., Bakst, H., Rinzler, S. H., Benjamin, Z. H., Warshaw, L. J., Bobb, A. L., Kwit, N. T., Modell, W., Rothendler, H. H., Messeloff, C. R., and Kramer, M. L.: A Method for the Evaluation of the Effects of Drugs on Cardiac Pain in Patients with Angina of Effort. A Study of Khellin (Visamin). Am. J. Med. **9:** 143 (Aug.), 1950.

Using a "daily report card" system for obtaining data, the authors found that oral doses of khellin (100 and 150 mg. daily) had no greater effect than a lactose placebo in controlling pain of angina of effort in 39 selected patients with coronary artery disease. Severity of the heart condition was evaluated on the degree to which pain interfered with the patient's capacity to carry on. The system consisted of having each subject note at the end of the day whether he had a "day same as usual," "bad day," "good day" and "day without pain." The authors recommend this method for the investigation of the effects of drugs on a symptom involving other organs and systems. Khellin caused no essential change in blood pressure. Unpleasant symptoms referable to the gastrointestinal tract or central nervous system were attributed to khellin in 33 per cent of the patients.

HARRIS

Masuoka, D. T., and Saunder, P. R.: Positive Inotropic Action of Ouabain on Rat Ventricle Strips. Proc. Soc. Exper. Biol. & Med. **74:** 879 (Aug.), 1950.

The authors report the first conclusive demonstration of a cardiotonic effect of ouabain on rat myocardium. When ouabain was added to the hypodynamic ventricle strip, there was a rapid increase in the force of contraction, reaching a maximum in three to five minutes. At a concentration of 1:40,000 of ouabain there was a pronounced positive inotropic effect, which remained above the zero value for more than four hours, whereas the force of contraction following the use of 1:8,000 ouabain solution returned to the zero time in about one hour. When the papillary muscle of the cat's heart was exposed to 1:5 million concentration of ouabain, the maximum tension was not reached until 45 to 90 minutes. The difference in time response to ouabain between the cat papillary muscle and the rat ventricle strip may be due to a species difference. The rat ventricle strip exhibited maximal contraction at a concentration of 0.062 per cent calcium chloride, and above or below this amount there was a decrease in activity.

In the presence of a low concentration of phosphate, ouabain produced the greatest effect. The highest concentration of phosphate produced the most rapid "fatigue," and even after ouabain was removed, this depressant effect of phosphate was apparent.

MINTZ

Huggins, R. A., Morse, R. A., Chapman, D. W., and Schuhmacher, L. F.: The Effect of Quinidine on Arrhythmias Induced by Cyclopropane and Cyclopropane-Epinephrine. Anesthesiology **11:** 623 (Sept.), 1950.

Dogs were anesthetized with cyclopropane and cardiac arrhythmias were induced by intravenous epinephrine. Intravenous quinidine sulfate or lactate markedly decreased the incidence of arrhythmias. The duration of the protection was roughly a function of the size of the dose of the drug, and the action became apparent in less than a minute after administration. The rapidity of the onset of the quinidine effect was independent of the dose.

WAIFE

Ziperman, H. H., Hughes, R. R., and Shumacker, H. B., Jr.: The Effect of Barbiturates and Other Drugs on Mortality from Diodrast in the Mouse. Angiology **1:** 427 (Oct.), 1950.

The authors studied fatal reactions to Diodrast in the mouse with particular reference to any beneficial influence of drugs or anesthetic agents upon toxicity. The dosage used was from ten to sixty times greater, on a body weight basis, than the amounts customarily used in studies on human patients. The authors were not concerned with sensitivity reactions. Nembutal, Barbital, Seconal, and Evipal all decreased the incidence of immediate deaths following the intravenous administration of Diodrast. Barbital and Nembutal in repeated dosage appeared to lower significantly the over-all mortality; ether anesthesia, morphine, Benadryl and intravenous procaine hydrochloride did not alter the fatal outcome following the administration of Diodrast. A dose of Diodrast, which was without any harmful effect in normal mice, was fatal if given to mice. shortly after bilateral ligation of the renal pedicles.

WESSLER

Smith, D. J., and Coxe, J. W.: Comparative Reactivity of Isolated Surviving Coronary Arteries to l-Epinephrine and l-Norepinephrine. Proc. Soc. Exper. Biol. & Med. **75:** 245 (Oct.), 1950.

The coronary arteries of healthy slaughtered swine were examined by the angioplethysmokymographic technic of Smith and Syverton. The vessels were removed and mounted in the plethysmograph and perfused with Tyrode's solution until the arterial wall assumed a certain degree of tone. The artery was then tested with l-epinephrine and l-norepinephrine by injecting test doses of usually 50 gamma of the drugs into the perfusate. Volume changes of the artery were recorded as a measure of constriction or dilatation. l-Norepinephrine produces about two and one-half times the degree of vasodilation produced by l-epinephrine in the same artery in the same dose. This difference exceeds the anticipated difference attributable to differing molecular weights.

MINTZ

Clagett, A. H., Jr.: Intravenous Use of Quinidine, with Particular Reference to Ventricular Tachycardia. Am. J. M. Sc. **220:** 381 (Oct.), 1950.

Quinidine lactate, supplied in 10 cc. ampules of 0.65 Gm. each, was administered intravenously by slow infusion to 13 patients for treatment of cardiac arrhythmias. After an initial trial using a larger volume of diluent, the author found it most convenient to add the contents of one ampule of quinidine lactate to 50 cc. of 5 per cent glucose in a 100 cc. flask. This solution was given intravenously at a rate of 2 cc. per minute under constant observation. If larger doses of quinidine were required, more of the solution was added to the flask. The required doses varied from 0.4 to 3.25 Gm. The cardiac arrhythmias treated included ventricular and auricular tachycardias, premature ventricular beats, auricular flutter, and auricular fibrillation. This method is considered safer than intramuscular or more concentrated intravenous injections, because the drug may be stopped immediately when the rhythm becomes normal or at the onset of toxic reactions. In this series, nausea and vomiting occurred in 3 patients during treatment; in 2 patients, the arrhythmias were unaffected, and they expired during quinidine therapy.

The author recommends that quinidine be added to the intravenous fluids during surgery involving cardiac manipulation at a rate of 0.2 Gm. every three hours; 4 patients so treated manifested no significant toxicity. In myocardial infarction complicated by ventricular tachycardia, quinidine given in this manner appeared to be effective and safe. Some of the more serious toxic reactions seen with intravenous (undiluted) quinidine, which were not present in this series of patients, are reviewed in the article.

SHUMAN

PHYSICAL SIGNS

Coulter, W. W.: Diagnosis of Primary Cardiac Neoplasms. Texas State J. Med. **46:** 596 (Aug.), 1950.

Primary neoplasms of the heart, unlike secondary ones, are uncommon. The most common primary neoplasm of the heart is the myxoma occurring usually in the left atrium. In common with other cardiac neoplasms, the most frequent symptom is that of intractable congestive heart failure. Rheumatic heart disease is the most frequent misdiagnosis in cases of tumor of the left atrium. The occurrence of symptoms resembling acute circulatory failure with spectacular relief on change in position is almost pathognomonic of either a pedunculated intracardiac neoplasm or a ball valve thrombus. The diagnosis of myxoma of the left atrium has assumed considerable importance since curative surgery may now be considered. Although rhabdomyomas and sarcomas may also be diagnosed when present, they are not amenable to surgery.

SCHWARTZ

Raleigh, G. W., and Stengle, J. M.: Mesosystolic Third Heart Sound. Quart. Bull., Northwestern Univ. M. School **24**: 176 (Fall), 1950.

The authors present 5 cases illustrative of the phenomenon of the mesosystolic third sound in the normal heart and review the pertinent literature. This sound, sometimes referred to as midsystolic click, is high pitched and of a distinct snapping or clicking quality. It may occur at any point between the first and second sounds, often resembles the latter in pitch and intensity, and is not infrequently encountered in the examination of normal hearts. It is heard best in the apical or mesocardiac areas and is to be distinguished from the uncommon, low pitched, basal midsystolic gallop sound, which probably occurs only in the presence of organic heart disease.

In the experience of the authors, most of the subjects displaying this sound were of slender body build with long chests and vertical hearts. All were young adults in good health. An apparently benign systolic murmur frequently preceded the click, and temporal variation, as well as alteration with respiration, exercise or positioning, were often apparent. The mode of production is unknown.

SCHWARTZ

PATHOLOGY

Spain, D. M., Bradess, V. A., and Parsonnet, V.: Myocarditis in Poliomyelitis. Am. Heart J. **40**: 336 (Sept.), 1950.

Myocarditis was found in 12 of 14 patients who died from poliomyelitis (including the spinal, bulbar, and bulbospinal types). Gross changes were found only in one heart whose myocardium was flabby and pale yellowish brown in color. Microscopically, the lesions were confined to the myocardium. There was poor staining of the myocardial fibers, and separation of these fibers by edema fluid and fibrin; diffuse, focal and perivascular collections of polymorphonuclear leukocytes, lymphocytes, occasional plasma cells and mononuclear cells; hemorrhage; focal necrosis; edema; fibrosis; and fibroblastic proliferation. In the cases of longer duration (22 days) considerable fibrosis was present and the cellular infiltration consisted predominantly of lymphocytes. Clinical evidence of myocarditis was present in one patient and consisted of a persistent rapid pulse rate of 160 although the temperature was normal. Terminally there was some degree of cardiac failure. The authors believe that the etiology of the myocarditis is specifically related to the poliomyelitis group of viruses.

HELLERSTEIN

RHEUMATIC FEVER

Barnes, A. R.: Effects of Cortisone and ACTH in 14 Patients with Acute Rheumatic Fever. Proc. Staff Meet. Mayo Clin. **25**: 478 (Aug.), 1950.

Cortisone was administered to 7 patients and ACTH to 3 patients in their first attack of rheumatic fever. After 1 to 10 months (average 5.9 months), 5 patients had no murmurs or cardiac enlargement and the remaining 5 had no cardiac enlargement but did have apical systolic murmurs. In 2 the character of the murmurs did not suggest the existence of a significant valvulitis. Four patients were treated for recurring attacks of rheumatic fever and were considered to have active carditis. The administration of cortisone was attended by a marked reduction in heart size in 2 patients and a moderate reduction in 1. It was concluded that cortisone can greatly improve the status of some patients with rheumatic carditis.

Cortisone and ACTH can effectively suppress the acute manifestations of rheumatic fever in three weeks or less, but it is very doubtful that they shorten the natural duration of the acute rheumatic state. Cortisone and ACTH were not observed to prevent recurrences of acute rheumatic fever or to modify pre-existing chronic valvular damage and associated cardiac hypertrophy.

SIMON

ROENTGENOLOGY

Kjellberg, S. R., and Olsson, S. E.: Roentgenological Studies of Experimental Pulmonary Embolism without Complicating Infarction in Dog. Acta radiol. **33**: 507 (June), 1950.

The authors introduced artificial emboli into the venous circulation of 9 normal dogs. Postmortem examination was made in all cases, the site of the pulmonary embolus determined, and its obstructive character verified. Eight dogs were subjected to roentgenologic examination and in one the lung was examined by surgical exposure. There were no changes in the roentgenograms after the lodging of the emboli. No changes were noted in the vascular design, or in the caliber of the artery on the peripheral side of the embolus, nor was any abrupt change of the vascular design seen. No local emphysema or other lung changes were seen. In all cases, the time of observation was two to four hours after the embolus was introduced. In one case where the chest was opened and the lungs were studied in situ and respiration was continued with additional pressure, no changes could be seen after the introduction of the embolus.

The authors conclude that these studies support the opinion that no roentgenologic changes in the lungs are observed in uncomplicated pulmonary embolism, and that no infarction will occur as long as the circulation through the bronchial artery is intact.

SCHWARTZ

Boyodjian, N.: A study of the Symptomatology of Enlargement of the Middle Segment of the Heart. Acta Clin. Belg. **5**: 335 (July–Aug.), 1950.

Roentgenologic enlargement of the left middle segment of the heart shadow is found in a variety of conditions. In mitral disease the segment is elongated, moderately prominent and sometimes has a double contour. Chronic cor pulmonale and congenital anomalies like interauricular septal defect, patent ductus arteriosus or Eisenmenger's complex show larger hilar shadows and enlargement of a single chamber, usually the right ventricle. Prominence of the pulmonary segment may be noted in vertical hearts with marked clockwise rotation, in some instances in association with idiopathic dilatation of the pulmonary artery. A "false" enlargement of the middle cardiac segment may be due to an arteriovenuos pulmonary aneurysm, to aneurysm of the descending aorta or to other extracardiac affections, such as enlarged lymph nodes, a thymus gland or a neoplasm of the mediastinum.

The author discusses the differential diagnosis of the various conditions which, in some instances, may require additional laboratory procedures like angiocardiography, cardiac catheterization or the rebreathing and oxygen utilization test.

PICK

Wiekbom, I.: The Influence of the Blood Pressure in Urographic Examination. Acta radiol. **34:** 1 (July–Aug.), 1950.

The author reports 2 cases in whom intravenous pyelography revealed no contrast filling of the renal pelvis when the blood pressure fell to shock levels. When the blood pressure was increased by intravenous ephedrine there was adequate visualization of the renal pelvis within two minutes in one case and in seven minutes in the second.

SCHWEDEL

Kammerling, E., Cavenagh, J. B., and Unger, L.: Cardiac Aneurysm Demonstrated by Angiocardiography. Illinois M. J., **98:** 129 (Aug.), 1950.

The authors present a case emphasizing the value of angiocardiography in the differential diagnosis of a mediastinal mass after ordinary clinical and roentgenoscopic methods had failed. The patient was a young woman whose chest x-ray showed a large mass adjacent to or continuous with the left ventricle. Serial electrocardiograms revealed alternate paroxysmal ventricular tachycardia and sinus rhythm with evidence of previous anterolateral myocardial infarction. Prior to angiocardiography, opinion was divided between the diagnosis of ventricular aneurysm, pericardial cyst, or extracardiac neoplasm invading the heart or pericardium. The levo-angiocardiogram, which revealed the greatly dilated left ventricular cavity, with dye filling most of the area under question, conclusively established the diagnosis of ventricular aneurysm.

SCHWARTZ

Pearl, F., Gray, M. and Friedman, B.: Retrograde Aortography with a Special Catheter Including Demonstration of the Coronary Arteries. Ann. Surg. **132:** 959 (Nov.), 1950.

The authors describe the method of passing a special thin-walled catheter into an artery, preferably the radial artery just below its origin, or the profunda, then upwards into the desired portion of the aorta. The outside diameter of the catheter is small enough to permit restoration of the artery by suture on its withdrawal. Selective arteriograms may be taken of any portion of the aorta by using only a few cc. of radiopaque liquid. The coronary arteries may be regularly demonstrated by this method.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Reboul, H., and Laubry, P.: Endarteriectomy in the Treatment of Chronic Endarteritis Obliterans of the Limbs and Abdominal Aorta. Proc. Roy. Soc. Med. **43:** 547 (July), 1950.

The authors performed 93 endarteriectomies for the treatment of chronic endarteritis obliterans after prolonged conservative therapy had failed. In all instances extensive arteriographic studies had been carried out previously in order to locate the exact site or sites of occlusion.

The obliterated segment of artery in each case was completely cleared of all adipose tissue and opened longitudinally for a distance of 4 to 6 cm. When the thrombus was exposed, a plane of cleavage was produced between the external elastic limiting layer and the media. Then the necrosed media, the internal elastic limiting layer, the intima and the thrombus were removed, leaving the external elastic limiting layer and the adventitia. The endarteriectomy was completed above and below by cutting through the inner arterial coats in a healthy zone and then the vessel was closed. During the entire operation the arterial bed was frequently irrigated by a heparin solution. Postoperatively heparin was given intravenously for the first three or four days.

In approximately half the cases complete relief of symptoms occurred. There were no signs to indicate that removing the various layers of the vessel weakened the wall to a dangerous degree, provided the external elastic limiting layer was in a healthy condition.

ABRAMSON

SURGERY IN HEART AND VASCULAR SYSTEM

McSwain, B., and Diveley, W.: Arterial Aneurysms. Ann. Surg. **132:** 214 (Aug.), 1950.

The authors report observations on 26 arterial aneurysms subjected to operation. In most instances a mass was palpable and pulsations were noted over it. A systolic bruit was likewise generally present, although a thrill was noted in only 8 instances.

With regard to operative procedures, complete aneurysmectomy was considered the method of choice. However, in the case of aneurysms of essential arteries, attempts were made to perform a reconstructive or restorative aneurysmorrhaphy, or if such a procedure was impossible, to obliterate the aneurysm by sutures placed within the sac. Sympathectomy was not done in any of the cases. One patient died on the operating table; the remainder survived the procedure. However, in 3 amputation was necessary shortly after operation. Nine patients died several months or years after operation.

ABRAMSON

Murray, G.: A Cardioscope. Angiology **1:** 334 (Aug.), 1950.

The author describes a cardioscope for use in intracardiac surgery. Through a cannula which prevents leakage of blood, the instrument can be passed or withdrawn at will and moved about freely within the heart chamber.

WESSLER

Stokes, T. L., and Gibbon, J. H., Jr.: Experimental Maintenance of Life by a Mechanical Heart and Lung during Occlusion of the Venae Cavae followed by Survival. Surg., Gynec. & Obst. **91:** 138 (Aug.), 1950.

The authors describe a procedure by means of which they were able to maintain life in a series of 8 dogs in which the venae cavae were completely occluded for a period of from 30 to 46 minutes. During this time the entire cardiorespiratory functions were maintained by the apparatus, consisting of a mechanical heart and lung.

It is believed that the experiments constitute a step toward the clinical application of such a procedure in patients with failing heart or lungs or in the problem of performing precise operations within the chambers of the human heart, under direct vision, and in a bloodless field.

ABRAMSON

Cassel, M. A.: Treatment of Post-Thrombotic Syndrome by Interruption of Superficial Femoral Vein. Arch. Surg. **61:** 540 (Sept.), 1950.

The author ligated the superficial femoral vein in 10 patients suffering from the post-thrombotic syndrome. In all instances the immediate results were satisfactory: the edema disappeared, the pain decreased, and ulcerations healed. Since the improvement could also have been due to the bed rest and the general hospital care incidental to surgical treatment, a follow-up study was carried out in 7 of the patients. Only 3 of these showed persistent reduction in edema, while relief of pain and improvement in stasis dermititis were consistently found. One ulcerated limb, which had healed after ligation, broke down again, with recurrence of the lesion. Two other ulcers remained healed.

Although the results could not be analyzed statistically because of the small number of cases in the series, it was the author's opinion that they appear to justify further investigation of the use of superficial femoral vein ligation in a disease which has generally failed to respond to the many other forms of treatment.

ABRAMSON

Child, C. G., Milnes, R. F., Holswade, G. R., and Gore, A. L.: Sudden and Complete Occlusion of the Portal Vein in the Macaca mulatta Monkey. Ann. Surg. **132:** 475 (Sept.), 1950.

The authors studied the effects of sudden and complete occlusion of the portal vein in 25 monkeys and in 2 patients with inoperable cancer. Nineteen of the animals operated upon survived uneventfully, as did the 2 patients. With regard to changes in cardiovascular dynamics following operation, there was an immediate fall in systemic blood pressure of about 20 to 30 mm. Hg and then a return to the pre-occlusive levels within one to four hours after ligation. Venous pressures definitely rose, and even after a week they had not returned to the pre-occlusive levels.

Through the use of portal venograms, it was found that immediately after ligation, portal blood gained access to the sytemic circulation primarily through pelvic anastomotic channels and through the hepatoportal vessels. At the end of about two months blood was gaining access to the liver directly, the site of occlusion or ligation of the portal vein being by-passed. The hepatoportal plexus of veins progressively expanded so that by the end of a year the portal blood traversed the liver normally. The authors conclude that the monkey, at least, can tolerate sudden division of its portal vein.

ABRAMSON

Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery. Ann. Surg. **132:** 531 (Sept.), 1950.

Using two blankets containing coils with circulating refrigerant, the authors dropped the body temperature of 39 dogs to 20 C.; they then excluded the heart from the circulation for periods of 15 minutes or more by applying clamps to the superior and inferior venae cavae and azygos vein. Nineteen animals died either during the clamp-off period or during warming. The remainder were returned to normal body temperature. Of the latter, 6 survived the procedure completely, and, after an initial period of lethargy and weakness, resumed apparently normal activity within a few days. The remaining 12 surviving dogs developed a state of shock in 2 to 12 hours, and subsequently died.

The authors are of the opinion that, with a greater knowledge of the physiology of hypothermia, it may be possible to endow nonhibernating mammals with the ability to survive even lower temperatures than

those tolerated thus far. Temperatures below 20 C. would further reduce the tissue oxygen requirements and would conceivably increase the length of time an animal could tolerate interruption of its circulation. If hypothermia could be developed as a safe surgical technic, it might be expected to extend the scope of surgery in other fields.

ABRAMSON

Leriche, R.: Causes of Failure of Suprarenalectomy and Ganglionectomy in Thrombo-Angiitis Obliterans on the Basis of 898 Operations. Angiology **1:** 432 (Oct.), 1950.

The author has performed 800 ganglionectomies with and without splanchnic section and 98 suprarenalectomies for thromboangiitis obliterans. With these two operations, alone or combined, excellent and lasting results have been obtained with increasing frequency. There have been a certain number of failures. Three recognizable causes for these poor results have been noted: (1) persistence of infected ulceration, (2) extensive thrombosis of main channels, and (3) combined venous and arterial thrombosis. The first of these can usually be overcome by meticulous attention to local treatment without amputation; the latter two are not amenable to any therapy.

WESSLER

Milanes, B., Stables, E. P., and Lastra, J. S.: Observations on Chronic Obstruction of the Abdominal Aorta. Surgery **28:** 684 (Oct.), 1950.

The authors present 13 cases of chronic obstruction of the abdominal aorta, the symptomatology of which is similar to Leriche's syndrome. The disease generally commences insidiously, with the main complaints being coldness and intermittent claudication of the lower extremities. Loss of sustained erection is a valuable sign in young patients. The physical findings consist of absent pulsations in the femoral arteries and absent or greatly diminished pulsations in both iliac vessels and the infra-umbilical segment of the aorta. There may be muscular atrophy with loss of hair and discoloration of the lower extremities. In the terminal stages, serious bilateral ulcerative or gangrenous lesions may be observed.

Aortography gives important information concerning the collateral circulation. The direct punctures of the abdominal aorta through the back is the best manner in which to carry out this procedure, since it gives exact information concerning the type of obstruction and its localization, and at the same time is an easy technic, devoid of complications.

Since the thrombosed segment of aorta acts as a reflex center capable of producing distant spasm, the treatment of this condition is resection of the terminal portion of the vessel and of both iliacs, preceded by one-sided sympathectomy and followed a week or so later by sympathectomy on the other side. Medical measures are useless and do not improve any of the symptoms.

ABRAMSON

Lowenberg, E. L.: Aneurysm of the Abdominal Aorta. Report of Two Cases Treated by "Cutis Grafting." Angiology **1:** 396 (Oct.), 1950.

Cutis grafting of two aortic aneurysms is described. The first patient died from rupture of the aneurysm six months postoperatively; the second patient is alive and working 16 months postoperatively. The author believes that the method will effectively reinforce the weakened aneurysmal sac and delay rupture.

WESSLER

THROMBOEMBOLIC PHENOMENA

Berry, F. B., and Bougas, J. A.: Agnogenic Venous Mesenteric Thrombosis. Ann. Surg. **132:** 450 (Sept.), 1950.

The authors present 13 instances of agnogenic venous mesenteric thrombosis. A number of possibilities have been suggested as etiologic agents in the production of this condition, among them being obstruction of venous blood flow by temporary kinking, volvulus, intussusception or hernia, infection and sepsis, and some change in balance of the hematologic elements concerned in coagulation. According to the authors, the last factor appears to be the best possibility.

Agnogenic mesenteric thrombosis often displays a prodromal period, indicated by a history of migrating thrombophlebitis, pulmonary infarcts, thrombophlebitis of the lower extremities, or vague abdominal discomfort of episodic character. The more acute symptoms are those of intestinal obstruction or, later in the course of the disease, those of peritonitis. A very common symptom is intense abdominal pain, often intermittent and colicky, and generalized or localized in one region of the abdomen. Generally it cannot be controlled by opiates. Vomiting is present in about half the cases. Blood in the stomach is a late sign. A frequent finding on examination is a striking disproportion between abdominal rigidity, which is often very slight or entirely absent, and the duration of the symptoms. Tenderness, however, is acute, whereas rebound tenderness is not seen in the first days of the condition. Distension occurs quickly, but frequently lacks tympanitic qualities, because the distended loops of intestine are filled with fluid and blood. Free fluid in the peritoneum is always present. Shock is rare and is a late, grave sign.

The treatment of agnogenic venous mesenteric thrombosis is operative and little time should be lost before surgery is performed. Anticoagulant therapy should be instituted promptly in the postoperative period, heparin being used initially.

ABRAMSON

Olwin, J. H., and Fahey, J. L.: Ac-globulin Levels in Thrombo-Embolism. Ann. Surg. **132**: 443 (Sept.), 1950.

Accelerator globulin or, as it is generally termed, Ac-globulin is essential to the normal physiologic clotting process. It enhances the rate of formation of thrombin when prothrombin is allowed to interact with thromboplastin and calcium, the amount of thrombin formed being relatively proportional to the quantity of Ac-globulin present. The latter, therefore, appears to be an accelerator of prothrombin conversion.

Using an adaptation of the two stage prothrombin method, the authors determined the Ac-globulin levels of 46 patients demonstrating various types of intravascular clotting. Thirty-seven in the series showed levels of 120 per cent or more at some time following the clinical onset. Whether this increase in Ac-globulin was the cause or the result of the thrombotic episode could not be determined.

ABRAMSON

Boyd, A. M.: The Diagnosis and Pathogenesis of Obliterative Vascular Disease of the Lower Extremities. Angiology **1**: 373 (Oct.), 1950.

The author discusses the differential diagnosis of intermittent claudication. He states that simple clinical observation of color changes on elevation and dependency, temperature gradients, and nutritional changes, together with oscillometry, will, for all practical purposes, reveal the extent and type of arterial disease. Occasionally it may be necessary to resort to arteriographic studies.

A review of the arteriographic findings and clinical features in over 1000 patients with deficiency of the circulation in the lower limbs showed that they could be classified into four main groups: (1) traumatic thrombosis; (2) juvenile obliterative arteritis; (3) primary popliteal thrombosis; (4) senile obliterative arteritis. Arterial thrombosis due to gross trauma occurs but is rare. Juvenile obliterative arteritis occurs in patients under 35 years of age. The degenerative process is bilateral, begins in the small arteries of the feet, ascends the limbs, and ultimately leads to extensive gangrene and amputation. A patchy superficial phlebitis usually precedes the arterial changes. Primary popliteal thrombosis also occurs in patients under the age of 35, and is probably related to injury. The thrombus is confined to the popliteal artery, the wall of which is normal. The course is benign. Senile obliterative arteritis is the inclusive term for the degenerative arterial changes commonly associated with increasing age and usually referred to under the term arteriosclerosis. It may occur at an early age and is responsible for more than 95 per cent of all arterial occlusion. There is seldom more than superficial necrosis or loss of the terminal phalanges of the toes; the distribution is symmetrical. Patchy phlebitis is absent.

WESSLER

Ratcliffe, A. H.: Clinical Grades of Intermittent Claudication. Angiology **1**: 438 (Oct.), 1950.

The author discusses the theories advanced to explain the pain of intermittent claudication, and asserts that the concept of the accumulation of metabolites in ischemic muscle best fits the observable facts. An exercise tolerance test is described. The test can be used to separate cases of intermittent claudication into three grades of clinical severity. The author believes this classification to be an important guide to therapy.

WESSLER

Gottlieb, P. M., Turnoff, D., Zimmerman, J. J., and Chamblin, W. D.: Idiopathic Thrombophlebitis Migrans with Unusual Manifestations. Ann. Int. Med. **33**: 1275 (Nov.), 1950.

The authors describe a 31 year old Negro man who, after repeated thrombophlebitic episodes over a period of 18 years, has a residual lymphedema of all four extremities, the abdominal wall, penis and scrotum, and recurrent massive pleural effusions. The clinical course, the protean manifestations, the biopsy studies, and examination of the edema fluid seem to be compatible with a diagnosis of an idiopathic migrating thrombophlebitis with secondary lymphatic obstruction and lymphedema. No examples of recurrent serous effusions of such magnitude as exhibited by this patient were found in the literature. In the absence of clinical and roentgenographic evidence for pulmonary infarction, it is reasonable to deduce that in this case the pulmonic and perhaps other intrathoracic veins are involved in this same thrombophlebitic process.

WENDKOS.

VASCULAR DISEASE

Huttmann, A.: The Prognosis of Valvular Disease of the Heart. Ztschr. f. d. ges. inn. Med. **5**: 363 (June), 1950.

The author presents an analysis, with special reference to the prognosis, of 230 cases of various types of valvular disease of the heart. The cases were observed over a period of 3 to 11 years, and their age varied between 3 and 81 years. In about 50 per cent no etiologic factor for the valve affection could be established.

More than half (58.7 per cent) of the patients, especially those with combined aortic and mitral lesions, were found to be of the asthenic type. Mitral involvement prevails in women and aortic involvement in men. The mortality due to heart failure is greater in men, while death from cerebral embolus occurred more often in females. The earliest complication was subacute bacterial endocarditis followed by congestive heart failure, auricular fibrillation, and cerebral embolus. The mortality rate of cases with congestive heart failure does not differ with the presence or absence of

auricular fibrillation but is high following cerebral embolization. Thirty-six per cent of the cases died within one year and 83 per cent within three years after the onset of decompensation.

PICK

Lindqvist, T.: A Case of Raynaud's Syndrome after Head Injury. Acta med. Scandinav. **138:** (Supp. 246) 116 (June), 1950.

The author reports the case of a young woman who developed repeated attacks of cyanosis of the digits of both hands and feet 17 days after she had sustained an injury to her head. It is his belief that the vascular changes could have been due to trauma to the anterior portion of the hypothalamus.

ABRAMSON

Mason, G. M. C., Hazard, J. B., Corcoran, A. C., and Page, I. H.: Experimental Vascular Disease Due to Desoxycorticosterone and Anterior Pituitary Factors. Arch. Path. **49:** 641 (June), 1950.

The authors compared the vascular pathology in rats made hypertensive by silk perinephritis, and by treatment with desoxycorticosterone and anterior pituitary extracts.

Silk perinephritis involving one kidney, with the other removed, resulted in advanced arteriopathy in the intrarenal arteries and arterioles, in the mesenteric and pancreatic arteries and in the small and medium-sized coronary vessels. The latter did not consistently follow the course of the hypertension, in contrast to the renal and mesenteric arterial damage. Hypertension preceded the appearance of arteriopathy, especially in reference to the renal lesions.

Desoxycorticosterone hypertension was followed by advanced arteriopathy in the coronary, the mesenteric, the small cerebral, and the small renal vessels. Cessation of treatment was followed by reduction of the hypertension, but the arterial lesions already present progressed.

Extracts of anterior pituitary gland caused gradual enlargement of the heart, kidneys and adrenals. The renal vascular lesions were necrotic and involved the small arteries, especially the juxtaglomerular apparatus, and the glomeruli. The renal lesions closely resembled those caused by desoxycorticosterone, but extrarenal arteritis was minimal.

The authors believe that renal arteriopathy is the end result of hypertension, regardless of the method of production. Desoxycorticosterone was the most effective agent causing the most serious vascular degeneration. Anterior pituitary extract was least effective. The authors believe their experimental lesions to be practically identical with those of human malignant nephrosclerosis.

GOULEY

Lynn, R. B.: Lack of Return of Vascular Tone in the Feet after Sympathectomy. Lancet **1:** 1108 (June), 1950.

The author reports a case in which vascular tone did not return to a sympathectomized foot, and, as a result, the patient complained of excessive warmth of his feet, particularly at night. The operation had been performed because of the presence of recurrent ulceration of both legs which had not responded well to excision and skin grafting. Blood flow studies revealed approximately a ninefold increase in local circulation in the foot immediately after operation. The augmented flow persisted at almost the same level for as long as four months. The explanation for the lack of return of vascular tone following sympathectomy could not be determined.

ABRAMSON

Lynn, R. B., and Barcroft, H.: Circulatory Changes in the Foot after Lumbar Sympathectomy. Lancet **1:** 1105 (June), 1950.

The effect of lumbar sympathectomy on blood flow in the feet and skin temperature in the toes was studied in 6 normal lower extremities and in 13 limbs with various degrees of arterial abnormality. Immediately after operation a marked increase in blood flow occurred, with the peak being reached a day or two later. There then followed a rapid recovery of tone in the vessels of the foot; by the sixth postoperative day the flow, which had initially risen from a preoperative average of 2.1 ml. per minute per 100 cc. of tissue to 20.0 ml., now fell to 8.5 ml. By the first to the third month following operation, the level had dropped to 4.9 ml. The same type of response was noted in both the normal and abnormal foot. In contrast, the skin temperature of the toes rose rapidly after operation and remained high for at least one to three months. The explanation for such a response in the fact of a fall in blood flow to the entire foot was not evident.

It was concluded that sympathectomy has a beneficial effect in acute emergencies, since it produces a marked vasodilatation lasting for a few days. In chronic cases its main value is in isolating and protecting the denervated vessels from strong central stimulation excited by cold and other noxious agents.

ABRAMSON

Goodman, J. I., Wasserman, S., Marcus, L. J., and Frankel, L.: A Study of Atherosclerosis in a Group of Diabetic Patients. Am. J. M. Sc. **220:** 30 (July), 1950.

The aim of this study is the early recognition of arteriosclerosis. Eighty-nine unselected outpatient diabetics were analyzed because of the known prevalence of the disease in such patients. As a result of this study it is claimed that the carotid sinus pressure test, supraclavicular pulsations and the discovery of plaques in the aortic arch by roentgenography are valuable signs of proximal

atherosclerosis. It is also maintained that calcification of the abdominal aorta and clinical evidence of occlusive vascular disease are of comparable value in the diagnosis of peripheral atherosclerosis.

In the dissection of five consecutive amputated limbs, it was found that the cause of occlusion of the arteries is a characteristic fibrotic proliferation of the intima. The term "arteriofibrosis obliterans" is recommended for this process.

DURANT

Lawrence, E. A., and Rumel, W. R.: Arteriovenous Fistula of the Lung. J. Thoracic Surg. **20:** 142 (July), 1950.

Two cases of arteriovenous fistula of the lung are described. Both patients demonstrated a pulmonary tumor by x-ray examination and a loud, harsh bruit in the region of the right axillary line. This was synchronous with systole of the heart and was markedly accentuated with deep inspiration. No thrill was felt in either case. In one patient there was cyanosis of the face, hands, and mucous membranes, slight clubbing of the fingers and toes, and a polycythemia. In the other patient, such changes were not present. In both cases the arteriovenous fistula was resected and recovery followed. The specimens consisted of a cystic structure into which both arteries and veins entered.

It was suggested that the effective size of the arteriovenous shunt determines the degree of unsaturation of blood returning to the left heart, the cyanosis, the secondary polycythemia, and the increased total volume, cell volume, and hemoglobin content of the blood.

ABRAMSON

Naide, M.: Intermittent Claudication Treated by Reducing Demand of Calf Muscles for Blood. J. A. M. A. **143:** 968 (July 15), 1950.

The author noted that most patients with intermittent claudication tended to start walking at the rate of 110 to 120 steps per minute, also the pace for normal subjects. When the pace was dropped to 90 to 105 steps per minute and the length of each step was shortened, the patients could walk much farther without experiencing pain and could reach their destination sooner, since they did not have to stop so often to rest. Two individuals learned to increase their walking ability four- or fivefold by holding the knee of the affected leg in a stiff or semistiff position and placing most of the weight on the other leg. The limp with which they walked presumably reduced the tension on the calf muscles of the ischemic limb.

ABRAMSON

Carroll, D.: Chronic Obstruction of Major Pulmonary Arteries. Am. J. Med. **9:** (Aug.), 1950.

The author discusses 5 cases of massive obstruction to the pulmonary arteries which produced chronic cor pulmonale. Clinically these were characterized by cyanosis, dyspnea, orthopnea, polycythemia, rightsided heart failure, and right axis deviation of the electrocardiogram. The writer describes as a new sign the absence of vascular markings in the left lung field of one patient which was of help in diagnosing complete obstruction of the left pulmonary artery. Right heart catheterization in 2 cases revealed high pressures with low cardiac outputs.

HARRIS

Edwards, E. A. : Thromboangiitis Obliterans in Women. New England J. Med. **243:** 290 (Aug.), 1950.

The author reports 6 cases of thromboangiitis obliterans in women, 2 of whom showed concomitant rheumatoid arthritis, while 1 gave a history of rheumatic fever. In none of the patients, however, was pathologic examination of the peripheral vessels possible. The patients were all young women who smoked. In each instance definite organic involvement of the major peripheral arteries was present, and in all but one, phlebitis had existed some time during the course of the disease.

According to the author, one or more forms of an angiitis of the larger peripheral vessels may be part of the rheumatic state.

ABRAMSON

Firstbrook, J. B.: Effect of Choline Chloride on Development of Atherosclerosis in the Rabbit. Proc. Soc. Exper. Biol. & Med. **74:** 741 (Aug.), 1950.

Fourteen adult male rabbits of various breeds received 1 Gm. of cholesterol in gelatin capsules six days a week. Five animals received in addition 1 Gm. of choline chloride in gelatin capsules six days a week. The remaining 9 rabbits served as controls. After nine weeks of cholesterol and choline administration, the rabbits were sacrificed and the aortas removed and fixed in 10 per cent formalin. The aortas were stained with Sudan IV and graded as unknowns into five arbitrary groups according to the area of the intima involved by atherosclerosis.

Twelve of the 14 rabbits showed an increase in the degree of atherosclerosis with increasing average blood cholesterol levels. Two rabbits whose degrees of atherosclerosis were less than would be expected from the blood cholesterol levels had the lowest initial weights of the group. The author has previously shown that animals of low initial weight tend to develop less atherosclerosis than animals of high initial weight, other factors being equal.

The 5 rabbits which received 1 Gm. of choline chloride did not differ significantly from the 9 control rabbits in average blood cholesterol levels, in body weight, or in the degree of atherosclerosis which developed.

MINTZ

VASCULAR DISEASE

Orbach, E. J.: A New Approach to the Sclerotherapy of Varicose Veins. Angiology **1**: 302 (Aug.), 1950.

The author states that it is undesirable to thrombose varicose veins in their entire length, but that only small sections should be occluded. For this type of sclerotherapy, only highly efficient sclerosing agents in doses not higher than 0.5 cc. are suitable. Sodium tetradecylsulfate administered by a special technic has been found by the author to be very satisfactory.

WESSLER

Perlmutter, H. D., and Wagner, D. H.: Arterial Thrombosis in the Newborn Infant. J. Pediat. **37**: 259 (Aug.), 1950.

The authors report a case of a newborn infant, apparently anoxic at birth, who developed impending gangrene of the right leg. There was a large slough on the right buttock and pulsation of the right femoral artery was never demonstrated. It was assumed that there was thrombosis of the common iliac vessel together with thrombotic involvement of the gluteal vessels. The child was treated conservatively with circulatory improvement of the right leg. However, mental retardation became the major problem. The possibilities of the brain damage being due to anoxia or thrombosis of the cerebral vessels were considered.

An analysis was made of the 47 cases of thrombosis in infancy reported in the literature. It is emphasized that therapy should be conservative and amputation should be avoided since collateral circulation will often develop in what appears to be a hopeless case.

MARGOLIES

Messinger, W. J., Porosowska, Y., and Steele, J. M.: Effect of Feeding Egg Yolk and Cholesterol on Serum Cholesterol Levels. Arch. Int. Med. **86**: 189 (Aug.), 1950.

In three experiments in which 24 subjects were fed varying amounts of egg yolk powder in addition to their regular diet, the majority exhibited an increase in their serum cholesterol values. In a fourth experiment, 5 subjects were fed cholesterol in a variety of forms, including egg yolk powder. Egg yolk powder proved to be more effective than preparations of pure cholesterol in elevating serum cholesterol values in most subjects. It is concluded that there is a substance, as yet unidentified, in egg yolk which elevates the cholesterol level in human serum. The amount necessary to produce this result is well above that in the quantity of egg yolk consumed in the ordinary diet.

BERNSTEIN

Pennock, L. L., and Minno, A. M.: Vitamin E in Treatment of Leg Ulcers. Angiology **1**: 337 (Aug.), 1950.

Among 15 patients with peripheral vascular disease, the administration of vitamin E failed to influence favorably the progress of the disease or to shorten the healing time of leg ulcerations. The vascular conditions treated were thromboangiitis obliterans, arteriosclerosis obliterans, chronic venous insufficiency, hypertensive ischemic ulcer, and frostbite.

WESSLER

Taylor, C. B., Baldwin, D., and Hass, G. M.: Localized Arteriosclerotic Lesions Induced in the Aorta of the Juvenile Rabbit by Freezing. Arch. Path. **49**: 623, 1950.

The authors devised a method of producing local degenerative changes in the aorta of rabbits. They inserted needles behind the abdominal aorta, lifting the vessel and creating a compression factor. Carbon dioxide, under pressure for freezing, was allowed to pass into the needles; the adjacent compressed aorta was quickly frozen. Sharply localized levels of aortic degeneration could thus be observed. Some rabbits were maintained postoperatively for 24 weeks. The degenerative lesion was a Monckeberg type of calcific medial arteriosclerosis. The almost immediate change was disintegration of the medial smooth muscle with localized aneurysmal dilatation of the aorta, followed by acute degeneration of the elastic lamellae. Only the internal and external elastic lamellae remained unchanged. The intervening zone of medial damage became heavily infiltrated by calcium in the third week. Adventitial sclerosis was marked in all cases.

Regeneration appeared, consisting of a thickening of the intima, in which first elastic tissue and then smooth muscle formed an inner sleeve as thick as the original media. Twenty weeks after freezing, calcification had been absorbed for the most part, but the media remained as a thin atrophied strip. The hypertrophied new intima replaced the media as the functional aortic coat.

GOULEY

Denolin, H., Lequime, J., and Jonnart, L.: Arteriovenous Pulmonary Aneurysm. Acta cardiol. **5**: 144, 1950.

The authors relate the case of a 19 year old patient presenting the clinical and radiologic picture of arteriovenous pulmonary aneurysm. The study of the circulatory function showed a cardiac output reaching 6.87 liters per minute, of which 3.12 liters (or 45 per cent) were shunted at the site of the aneurysm. During an exercise test, there was a decrease in the ratio of oxygen utilization (ventilatory equivalent) and a desaturation of the arterial blood in oxygen. What these facts mean and how they are related is discussed; during exercise there probably is an increase of the shunt between the pulmonary artery and veins.

AUTHORS

Cross, K. W., and Wilson, G. M.: The Circulatory Changes Associated with Aneurysm of the Axillary Artery and Clubbing of the Fingers. Clin. Sc. **9:** 59, 1950.

The authors present a case of gross unilateral clubbing of the fingers associated with a syphilitic aneurysm of the distal part of the right axillary artery. The pressure in the digital arteries was found to be consistently higher in the fingers of the right hand than in those of the left. Blood flow in the right hand was considerably greater than that in the left, although in the forearms, the difference was only slight.

According to the author, the slight degree of clubbing in the left hand could be attributed to cirrhosis of the liver and pulmonary fibrosis, while the greatly increased clubbing in the right was largely a consequence of the axillary aneurysm. It is suggested that the augmented distal arterial flow which resulted in the fingers receiving more blood than required for heat elimination or nutrition of the tissues, led to the development of the anatomic changes associated with clubbing of the fingers. The physical mechanism whereby an aneurysm produces an increased distal circulation was difficult to elucidate.

ABRAMSON

OTHER SUBJECTS

Manning, G. W.: Cardiac Manifestations in Friedreich's Ataxia. Am. Heart J. **39:** 799 (May), 1950.

The case histories of 4 patients with typical Friedreich's syndrome and cardiac involvement are presented. An additional 2 cases are discussed who had variants of this disease, but no cardiac abnormalities. The familial nature of the disease was obvious in 5 of the 6 cases reported. Cardiac manifestations included acute heart failure, irregularity of the heart beat due to paroxysmal tachycardia, auricular and ventricular premature beats, and electrocardiographic changes in the RS-T complex, usually in leads II and III, associated with right axis deviation.

The author believes that there is a close similarity, both clinically and pathologically, between Friedreich's ataxia and familial cardiomegaly. It would appear that the lethal gene may result in true Friedreich's ataxia, Friedreich's ataxia associated with the cardiac disorders, variants of Friedreich's ataxia, intermediate forms of the degenerative processes within the central nervous system, and in cardiac disease only (the familial cardiac group).

HELLERSTEIN

Lian, C., and Charlier, R.: Experimental and Clinical Study of Khellin. Acta cardiol. **5:** 373, 1950.

From experiments reported in the literature and from personal observations on dogs, the authors arrived at certain conclusions concerning the pharmacodynamic action of khelline. It causes a general relaxation of the smooth musculature of the viscera and of the blood vessels, especially of the coronary arteries. The effect upon the latter is long acting and produced by only one-fourth of the dosage necessary to produce transient hypotension due to general vasodilation. The action of khellin upon the coronary arteries is about four times as powerful as the action of aminophylline. Khellin prevents ventricular fibrillation produced by adrenaline during chloroform narcosis in animals.

Khellin given intravenously, intramuscularly, or orally is rapidly absorbed and equally distributed throughout the tissues. Its excretion occurs slowly, as evidenced by its presence in the blood six to seven days following injection. Out of 200 patients with angina pectoris, 150 responded well to treatment with khellin (50 to 100 mg. daily by intramuscular injection). Since khellin is the most powerful known coronary vasodilator, it is recommended by the author for the treatment of myocardial infarction.

PICK

Raab, W., and Lepeschkin, E.: Cardiac Effects of n-Alkyl Homologues of Epinephrine (n-Isopropyl- and n-Ethyl Epinephrine). Cardiologia **16:** 332, 1950.

The author studied the effect of two vasodepressor n-alkyl homologues of epinephrine upon the electrocardiogram of cats in Nembutal anesthesia and under artificial respiration.

The effects of n-isopropyl epinephrine (Isupral) and to a lesser extent, of n-ethyl epinephrine resemble those of epinephrine or norepinephrine by producing cardiac acceleration and, in most instances, first flattening and later elevation of T waves. Cocaine diminished the effect upon the heart rate and accentuated the depressing effect upon the T wave. Dihydroergotamine increased and nitroglycerin decreased the cardioacceleratory effect of the n-alkyl homologues, but both, in contrast to their usual counteraction against changes induced by epinephrine or Arterenol, intensified the depressing effect on the T wave.

PICK

Solomon, C., McNeile, H. J., and Lange, R.: Experience with the New Anticoagulant, B. O. E. A. J. Lab. & Clin. Med. **36:** 19 (July), 1950.

This product, bis-3,3′-(4-oxycoumarinyl) ethyl acetate, [3,3′-carbethoxymethylene bis(4-hydroxycoumarin)] is chemically similar to dicumarol and is known under the trade name as Tromexan; the British have called it B.O.E.A. B.O.E.A. is administered orally and its effects can be followed in the laboratory, as can those of dicumarol, by prothrombin times. It is four times more soluble than dicumarol, more rapidly absorbed, more rapidly excreted, and of lower toxicity. The range of initial dosage necessary to achieve a therapeutic level

(arbitrarily defined as a prothrombin time of 25 sec.) was found to be 1.2 to 1.8 Gm. Therapeutic levels were obtained within 24 hours of administration, often in 16 hours. The range of the required maintenance dosage was found to be 0.3 Gm. to 0.9 Gm. In some instances elevation of the prothrombin time was noticed on the fourth day of treatment, and for this reason the maintenance dose was reduced on the third day. Fluctuation of the prothrombin time was minimized by a divided eight-hour dosage schedule. On a divided dosage maintenance schedule, prothrombin times returned to normal within 24 hours after the drug was discontinued. No toxicity was demonstrated except for a single episode of microscopic hematuria.

MINTZ

Dotter, C. T., Payne, M. A., and O'Sullivan, W.: Catherization of the Portal Vein in Man following Porto-caval Anastomosis. Ann. Surg. **132:** 310 (Aug.), 1950.

A method was described for the introduction of a cardiac catheter into the portal vein after surgical creation of a portocaval anastomosis. Under sterile precautions the catheter was introduced via the left saphenous vein into the inferior vena cava. It was manipulated under fluoroscopic control until the tip lodged in a position at the level of the twelfth dorsal vertebra and somewhat to the right of the position normally occupied by the inferior vena cava. A radiopaque material was then injected through the catheter, and, as a result, numerous vascular channels, which arborized in the region of the liver, were visualized. These joined together into a large trunk which entered the inferior vena cava. The advantage of such a procedure is that it affords a direct method by which portal vein blood may be investigated in the unanesthetized patient. Basic information can be collected concerning changes in portal blood under a variety of experimental conditions. Furthermore, the procedure should be of value in determining the patency of a portocaval anastomosis.

ABRAMSON

Lorenz, T. H., Kurtz, C. M., and Shapiro, H. H.: Cardiopathy in Friedrich's Ataxia (Spinal Form of Hereditary Sclerosis). Arch. Int. Med. **86:** 413 (Sept.), 1950.

The authors review the literature on the cardiac complications of Friedrich's ataxia and report their findings on 5 siblings. Their cases showed systolic murmurs, heart enlargement in some patients, and flat to inverted T waves in one or another of the electrocardiographic leads, findings which are similar to those reported in this disease by previous investigators. The theories for the production of these cardiac changes are discussed, but no conclusions are reached.

BERNSTEIN

Scarborough, W. R., Beser, J., Talbot, S., Mason, R. E., Singewald, M. L., and Baker, B. M.: A Method for Recording Ballistocardiographic Vectors. Preliminary Report. Bull. Johns Hopkins Hosp. **87:** 235 (Sept.), 1950.

The authors describe a new method for recording ballistic complexes in three positions, i.e., head-foot, lateral, and anterior-posterior directions. The ballistocardiograph had previously been used largely to record only those body vibrations directed parallel to the long axis of the body, yielding head-foot (H-F) records.

The method described employs a light wooden turntable which is placed on the flat upper surface of the ballistocardiograph bed's moving platform. The turntable can be rotated through 360° with respect to the long axis of the ballistocardiograph bed, and the record is taken in the usual manner. Records of the three positions cannot, however, be taken simultaneously, thereby diminishing the degree of fidelity of the vector loops. The authors maintain, however, that if respiration is suspended at the same approximate point in the respiratory cycle in each position, the consistent complexes in each of the records may supply a rough approximation of the vector loops. A simultaneously recorded electrocardiogram on each of the three records supplies a cardiac time reference.

The authors feel that there is no justification in suggesting that body motions delineated by the vector loops are related solely to cardiovascular phenomena; however, they feel that studies in progress on the elastic properties and mechanical couplings of the body may shed light on the problem. They feel that tridirectional recording has value as an empiric tool and should be considered simply an extension of ordinary head-foot recording allowing more parameters for clinical correlation.

Mathers, J. A. L., Nickerson, J. L., Fleming, T. C., and Patterson, M. C.: Abnormal Ballistocardiographic Patterns in Cardiovascular Disease as Recorded with the Low-Frequency Critically Damped Ballistocardiograph. Am. Heart J. **40:** 390 (Sept.), 1950.

The authors have studied the ballistocardiographic patterns of 16 patients with heart disease with the idea of (1) correlating pattern type with specific disease processes, and (2) correlating changes in a series of records with variations in clinical condition following treatment. Four patients had coronary heart disease; 3, cor pulmonale; 3, hyperthyroidism; 2, hypertension; 2, rheumatic heart disease; and 2, severe anemia with cardiac failure. Observations were made for a period of three to six weeks, with a follow-up study of six to ten months. Although a damaged myocardium was found in general to produce an abnormal ballistocardiographic pattern, there was no definite correlation between specific disease entities and the mechanical functions of the heart as demonstrated by the ballistocardiographic

pattern. Since normal patterns are occasionally found in cases of heart disease, and since abnormal records are found in 15 per cent of presumably normal individuals, the authors feel that the isolated finding of pattern abnormality does not constitute definite evidence of heart disease. The final decision should be based on clinical judgment. In those cases where there was clinical improvement in cardiac function, there was an improvement of the ballistocardiographic tracing toward a normal pattern type. Serial records, therefore, provide an objective method of evaluating therapy designed to improve the mechanical efficiency of the myocardium.

HELLERSTEIN

Kasner, E., and Hersh, J. B.: The Electronic Oscillometer. Angiology **1:** 391 (Oct.), 1950.

The authors describe an electronic oscillometer and digital inflation cuff. This apparatus, in addition to performing all the functions of the mechanical oscillometer, is more sensitive than the latter instrument and can be used to determine oscillometric indices anywhere on the limbs or digits.

WESSLER

Rabwin, M. H., and Merliss, R.: Surgical Relief of Epilepsy Associated with Carotid Sinus Syndrome. J.A.M.A. **144:** 463 (Oct.), 1950.

A man aged 51 suffered for 20 years with convulsive attacks of both petit and grand mal types which were brought on by turning his head or pressure on the neck. Careful studies made it apparent that three separate factors were operative in his case: postural hypotension, a hyperactive carotid sinus syndrome, and a convulsive diathesis. Four days after denervation of the left carotid sinus the patient had one petit mal attack, and in the following six months he had sixteen grand mal attacks. After this he passed through a seven year period without any convulsive seizures. He was studied again because of a number of fainting spells during a period of great emotional strain. It was decided that these were due to vasomotor instability and postural hypotension and not related to reestablishment of hyperactive carotid sinus. It is suggested that physicians search for this mechanism among all their epileptic patients; on occasion they will be rewarded by finding a surgically amenable type of the convulsive syndrome.

KITCHELL

Bell, R. H., Swigart, L. L., and Anson, B. J.: The Relation of the Vertebral Artery to the Cervical Vertebrae. Quart. Bull., Northwestern Univ. M. School **24:** 184 (Fall), 1950.

In a study of 200 cadavers it was found that, as regularly described, the most common site of vertebral entry of the vertebral artery was the sixth cervical vertebra. Next in order of decreasing frequency was entry at the level of the fifth and seventh cervical vertebra. Least common was entry into the foramen of the fourth cervical vertebra. In no specimen in the 200 examined did entry occur superior to the level of the fourth cervical vertebra. It is pointed out that these observations are significant clinically in relation to angiographic demonstration of intracranial arterial aneurysms, to the procedure of removing a cervical herniated pulposus, and to that of excising a neuroma.

SCHWARTZ

Osler, K. A.: Influence of Castration on Blood Pressure. Cardiologia **16:** 329, 1950.

The author studied by the plethysmographic method changes of blood pressure occurring in adult rats following castration. Males invariably showed an average transient elevation of 15 mm. Hg while females reacted with a definite fall in blood pressure (average, 13 mm.). The author discusses as a possible explanation for this observation, disturbances in the extracellular fluid balance or hormonal influences.

PICK

Lenal, R., Strauss Jr., J., and Schlichter, J. G.: Clinico-Pathologic Study of Rheumatic Heart Disease. Acta cardiol. **5:** 41, 1950.

A study of 300 autopsied cases of rheumatic heart disease led the authors to several conclusions They state that myocardial lesions, as contrasted with valvular deformities, play the predominant role in rheumatic heart disease. As proof, the authors observe that (a) the cause of heart failure and death in all cases of acute rheumatic fever was an acute myocarditis; (b) heart failure during the course of bacterial endocarditis was common and nearly always associated with an acute myocarditis accompanied by small infarcts; (c) heart failure and death during pregnancy or immediately following delivery was usually associated with acute rheumatic myocarditis, while many women with severe valvular deformities had uncomplicated pregnancies; (d) 18 per cent of patients over 50 years of age had severe valvular deformities but no cardiac symptoms were present during life and (e) extensive myocardial fibrosis was a more constant finding than severe valvular deformities in patients developing chronic heart failure.

Embolization occurred in 41 per cent of the patients in the absence of auricular fibrillation, always, however, in the presence of heart failure. The formation of mural thrombi was considered more closely related to heart failure than to auricular fibrillation.

LUISADA

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EDUCATIONAL MATERIALS

The Association has recently issued several new educational pamphlets intended primarily for the general public. Physicians may be interested in making these available to their patients. A complete list of educational materials for the lay public as well as for the physician and professional groups may be obtained by writing to the Association.

Among the new materials is "Your Blood Pressure and Your Arteries," a popular pamphlet on hypertension and arteriosclerosis, recently published by the Public Affairs Committee, and available through the Association. A question-and-answer leaflet, "What You Should Know about Rheumatic Fever," states the elementary facts. A pamphlet entitled "What the Classroom Teacher Should Know—and Do—About Children with Heart Disease," deals with problems that arise in school.

Dr. H. M. Marvin's summary pamphlet, "Challenge of Heart Disease," has recently been revised, as has the pamphlet, "Rheumatic Fever—Childhood's Greatest Enemy."

A new 16 mm. black-and-white sound film, "Guard Your Heart," features a doctor's advice and instructions to a middle-aged business executive. This film may be purchased from the Bray Studios, New York, or may be rented from some affiliated Heart Associations.

AMERICAN COUNCIL ON RHEUMATIC FEVER

The American Council on Rheumatic Fever will hold its Annual Meeting in Atlantic City, N. J., on Sunday, June 10, 1951, at 2:00 P.M., following the Association's Annual Meeting and Scientific Sessions, June 6–10, at the Chalfonte-Haddon Hall Hotel.

ASSEMBLY PANELS

In conjunction with the Association's Annual Meeting, six Assembly Panel Committees will hold discussions on Wednesday June 6, at 2:00 P.M. and 8:00 P.M. The Panel Committees and their Chairmen are as follows:

Research, Kenneth G. Kohlstaedt, M.D., Lilly Clinic, Indianapolis General Hospital; Community Services, William A. Brumfield, Jr., M.D., Deputy Commissioner, New York State Department of Health, Albany, N. Y.; Fund Raising, A. W. Robertson, Chairman of the Board of the Association; National, State, Chapter Relationships, Howard B. Sprague, M.D., President of the Association, Boston; Membership Policies, Louis N. Katz, M.D., President-Elect, Chicago; Education, Co-Chairmen: Clarence E. de La Chapelle, M.D., Associate Dean, New York University Post Graduate Medical School, and Ira V. Hiscock, Sc.D., Professor of Public Health, Yale University.

RESEARCH COMMITTEE

Dr. Francis C. Wood, Professor of Medicine, University of Pennsylvania School of Medicine, has been elected Chairman of the Research Committee of the Scientific Council for a period of three years to succeed Dr. Louis N. Katz, Chicago, beginning June 1951. Dr. Eugene A. Stead, Jr., Professor of Medicine, Duke University, has been elected Vice-Chairman of the Committee for a period of one year.

NEW AFFILIATES

The Idaho and Ohio Heart Associations have become affiliated with the Association. The Ohio Association will consolidate as chapters six regional Associations which previously were

directly affiliated with the A.H.A. They are Akron District Heart Association; Central Ohio Heart Association, Columbus; Cleveland Heart Society; Heart Council of Greater Cincinnati; Northwestern Ohio Heart Association, Toledo; Youngstown Area Heart Association.

INTERNATIONAL SOCIETY OF ANGIOLOGY

The International Society of Angiology will hold a meeting on June 9, 1951, at the Claridge Hotel, Atlantic City, N. J. The meeting will be devoted to a scientific program and a business session. Further information may be obtained from Dr. Henry Haimovici, Secretary, 105 East 90 Street, New York 28, N. Y.

EUROPEAN SOCIETY OF CARDIOLOGY

The European Society of Cardiology has been organized with the intention of bringing into one international body the Societies of Cardiology in all the European nations. Its stated objectives are "to foster the development of cardiology, to further scientific exchanges and to help personal contacts of those working in this specialty." The administration will be entrusted to a General Assembly of delegates of the various National Councils, who will elect a Council of officers. The Assembly will meet at least every two years. If possible, a biennial Congress will be organized to promote the Society's activities and maintain close collaboration among members.

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*Overman, W. J.; Gordon, W. H., and Burch, G. E.: Tracer Studies of the Urinary Excretion of Radioactive Mercury following Administration of a Mercurial Diuretic, Circulation *1*:496, 1950.

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